UNIVERSITY OF ALBERTA

THE LONG-TERM EFFECTIVENESS OF ANTIMALARIALS IN RHEUMATIC DISEASES

BY

JUAN ANTONIO AVIÑA-ZUBIETA ©

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The undersigned certify that they have read, and recommended to the Faculty of Graduate studies and research for acceptance, a thesis entitled Long-term effectiveness of antimalarials in rheumatic diseases. Submitted by Juan Antonio Aviña-Zubieta in partial fulfillment of the requirements for the degree of Master of Science in Experimental Medicine.

Dr. Anthony S. Russell
Supervisor

Dr. Ronald Casey

Dr. Stephen Newman

Dr. Maria E. Suarez-Almazor

Date: November 26 1996

UNIVERSITY OF ALBERTA

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NAME OF AUTHOR: JUAN ANTONIO AVIÑA-ZUBIETA

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November 27, 1996

Leandro Valle Entrada D Interior 416
Nonoalco Tlatelolco
Mexico, D.F. 06900
MEXICO.

To my wife Griselda, for her love, trust and her encouragement; to my parents especially my father for sharing the loneliness of the distance; finally to my daughter Ana Michelle for her patience.

ABSTRACT:

The purpose of this study was to compare the long-term effectiveness between chloroquine (CQ) and hydroxychloroquine (HCQ).

Medical charts of all patients seen by 9 rheumatologists and initiating antimalarial therapy between January 1985 and December l993 were reviewed. Demographic, disease, and therapy information were collected. The main outcome measure was the cause of AM discontinuation.

After all medical records were reviewed, 1042 eligible cases were identified. From these, 940 (90%) had usable information and they represent the cohort. Five hundred and fifty-eight had rheumatoid arthritis, 178 had systemic lupus erythematosus, 127 had palindromic arthritis, and 77 had other diagnoses. Fifty-seven percent of the patients received CQ and 43% HCQ. The proportion of patients with side effects on HCQ and CQ was 15% and 28% respectively ($p< 0.001$). Using Cox-regression model to adjust for age at the onset of antimalarial therapy, gender, disease type, duration of disease prior to therapy, physician differences, and rank selection, there were no differences in the hazard ratio for overall discontinuations between CQ and HCQ. However, the hazard ratio for discontinuation due to toxicity was lower for HCQ (HR= 0.62; 95% CI 0.40-0.96). Finally, the hazard ratio for discontinuations due to inefficacy was significantly higher for HCQ (HR= 1.44 95% CI 1.06-1.96). Given the apparent differences in efficacy and toxicity between the two drugs potential trade-offs between

increased toxicity, and vice versa, should be carefully considered by the patient and physician when selecting one of the two drugs.

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TABLE ON CONTENTS

	PAGE
CHAPTER 1. INTRODUCTION	1
GENERAL DESCRIPTION OF ANTIMALARIALS	
1. Pharmacokinetics of antimalarials	2
2. Mechanism of action	4
CHAPTER 2. REVIEW OF THE LITERATURE: EFFICACY AND TOXICITY OF ANTIMALARIALS	6
1. Antimalarials as antirheumatic drugs	7
2. Antimalarials in rheumatoid arthritis	8
3. Antimalarials in systemic lupus erythematosus	12
4. Antimalarials in other rheumatic diseases	14
5. Chloroquine versus hydroxychloroquine	14
6. Antimalarials patterns of prescription	16
CHAPTER 3. RATIONALE AND OBJECTIVES OF THE STUDY	17
1. Limitations of previous studies	18
2. Objectives and hypothesis	21
2.1 Descriptive objectives	22
2.2 Analytic objectives	22
2.3 Hypotheses	22
3. Relevance of this study	22
CHAPTER 4. PATIENTS AND METHODS	24
1. Design of the study	25
2. Selection of the study cohort	25
2.1 Initial selection of potential cases	26

2.2 Review of medical charts 27
2.3 Definite inclusion in the cohort 27
3. Extraction of medical chart information 27
4. Study variables 28
5. Statistical methods 29
5.1 Bivariate analyses 29
5.2 Multivariate analyses 30

CHAPTER 5. RESULTS 1 32
CHARACTERISTICS OF THE COHORT
1. Initial selection of the cohort 33
1.1 Demographic characteristics 33

CHAPTER 6. RESULTS 2 39
ANTIMALARIAL DISCONTINUATIONS 40
1. Antimalarial discontinuations 40
2. Survival time analysis 40
3. Side effects 45
4. Summary 46

CHAPTER 7. RESULTS 3
MULTIVARIATE ANALYSIS COX'S REGRESSION 90
1. All causes of discontinuation 93
2. Discontinuations due to toxicity 94
3. Discontinuations due to inefficacy 95

CHAPTER 8. CONCLUSIONS AND DISCUSSION 111
1. Overall rates of discontinuation 113
2. Discontinuations and adjustment for time 114
3. Multivariate analysis 115

BIBLIOGRAPHY 119

APPENDIX 1: Forms to collect the data 127

LIST OF TABLES

TABLE	DESCRIPTION	PAGE
1	Demographic data of the patients included in the cohort	36
2	Demographic data by disease group	37
3	Disease duration at the onset of antimalarial therapy among diseases.	38
4	Causes of discontinuation for antimalarials in general and by type of antimalarial.	48
5	Mean times of discontinuation between chloroquine and hydroxychloroquine.	49
6	Mean times of discontinuation among all disease groups.	50
7	Mean time of discontinuation among rheumatologists.	51
8	Side effects between antimalarials.	52
9	Side effects outcome	53
10	Cox regression model (univariate) with all causes of discontinuation as dependent variable.	99
11	Cox regression model (all variables) with all causes of discontinuation as the dependent variable.	100

TABLE	DESCRIPTION	PAGE
12	Cox regression model (best model) with all causes of discontinuation as dependent variable.	101
13	Cox regression model (best model with interactions) with all causes of discontinuations as dependent variable.	102
14	Cox regression model (univariate) with discontinuations due to toxicity as the dependent variable.	103
15	Cox regression model (all variables) with discontinuations due to toxicity as the dependent variable.	104
16	Cox regression model (best model) with discontinuations due to toxicity as the dependent variable.	105
17	Cox regression model (best model with interactions) with discontinuations due to toxicity as the dependent variable.	106
18	Cox regression model (univariate) with discontinuations due to inefficacy as the dependent variable.	107
19	Cox regression model (all variables) with discontinuations due to inefficacy as the dependent variable.	108
20	Cox regression model (best model) with discontinuations due to inefficacy as the dependent variable.	109

TABLE	DESCRIPTION	PAGE
21	Cox regression model (best model with interactions) with discontinuations due to inefficacy as the dependent variable.	110

LIST OF FIGURES

FIGURE	DESCRIPTION	PAGE
1	Kaplan-Meier for all causes of discontinuations for any AM.	54
2	Kaplan-Meier for discontinuations due to toxicity for any AM.	55
3	Kaplan-Meier for all causes of discontinuations due to inefficacy for any AM.	56
4	Kaplan-Meier curves for all causes of discontinuations between chloroquine and hydroxychloroquine	57
5	Kaplan-Meier curves for discontinuations due to toxicity between chloroquine and hydroxychloroquine.	58
6	Kaplan-Meier curves for discontinuations due to inefficacy between chloroquine and hydroxychlroquine	59
7	Kaplan-Meier curves for all discontinuations by disease group.	60
8.	Kaplan-Meier for toxicity among disease groups.	61
9.	Kaplan-Meier for inefficacy among disease groups.	62
10	Kaplan-Meier for all causes of discontinuation for rheumatoid arthritis by type of antimalarial.	63

11 Kaplan-Meier curves for toxicity in rheumatoid arthritis and by type of antimalarial. 64

12 Kaplan-Meier curves for inefficacy in rheumatoid arthritis and by type of antimalarial. 65

13 Kaplan-Meier curves for all discontinuations in SLE by drug. 66

14 Kaplan-Meier curves for toxicity in SLE by drug. 67

15 Kaplan-Meier curves for inefficacy in SLE by drug. 68

16 Kaplan-Meier curves for all causes of discontinuation in palindromic arthritis by drug. 69

17 Kaplan-Meier curves for toxicity in palindromic arthritis by drug. 70

18. Kaplan-Meier curves for inefficacy in palindromic arthritis by drug. 71

19 Kaplan-Meier curves for all causes of discontinuation among rheumatologists. 72

20 Kaplan-Meier curves for toxicity discontinuations among rheumatologists. 73

21 Kaplan-Meier curves for inefficacy discontinuations among rheumatologists. 74

FIGURE	DESCRIPTION	PAGE
22	Kaplan-Meier curves for males by type of antimalarial.	75
23	Kaplan-Meier curves for females by type of antimalarial.	76
24	Kaplan-Meier curves for males by type of antimalarial	77
25	Kaplan-Meier curves for females by type of antimalarial	78
26	Kaplan-Meier curves for discontinuations due to inefficacy in males by drug.	79
27	Kaplan-Meier curves for discontinuations due to inefficacy in females by drug.	80
28	Kaplan-Meier curves for discontinuations due to inefficacy by drug and disease duration.	81
29	Kaplan-Meier curves for inefficacy discontinuations by type of antimalarial and disease duration.	82
30	Kaplan-Meier curves for discontinuations due to toxicity by drug and disease duration.	83
31	Kaplan-Meier curves for discontinuations due to toxicity by drug and disease duration.	84

FIGURE	DESCRIPTION	PAGE
32	Kaplan-Meier curves for discontinuations due to inefficacy by drug and disease duration.	85
33	Kaplan-Meier curves for inefficacy discontinuations by type of antimalarial and disease duration of more than 2 years.	86
34	Kaplan Meier curves for all causes of discontinuations by rank selection.	87
35	Kaplan-Meier for discontinuations due to toxicity by rank.	88
36	Kaplan-Meier for first rank selection by type of antimalarial.	89
37	Graph of log {-log [S(t)] } against log time by type of antimalarial for all causes of discontinuations	96
38	Graph of log {-log [S(t)] } against log time by type of antimalarial for toxicity discontinuations	97
39	Graph of log {-log [S(t)] } against log time by type of antimalarial for inefficacy discontinuations	98

ABBREVIATIONS

AM:	Antimalarials
RA:	Rheumatoid arthritis
SLE:	Systemic lupus erythematosus
PA:	Palindromic arthritis
CQ:	Chloroquine
HCQ:	Hydroxychloroquine
NSAIDs	Nonsteroidal antiinflamatories
HR	Hazard ratio

CHAPTER 1

INTRODUCTION

GENERAL DESCRIPTION OF ANTIMALARIALS

Antimalarials (AM) have become one of the most commonly prescribed drugs in the treatment of many rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), palindromic arthritis, and psoriatic arthritis among others (1). This appears to be related to the low dropout rate and their low toxicity in comparison to other antirheumatic drugs (2-5). Although there is considerable knowledge in relation to the mechanism of action of AM, the ultimate factor(s) are still unknown. The available evidence suggest that AM have multiple effects including non specific anti-inflammatory effects, inhibition of the secretion of pro-inflammatory cytokines, inhibition of antigen processing and presentation which is perhaps the most important one which differentiates AM from nonsteroidal aniitinflammatories (NSAIDs) (6-7). The antimalarial effect does not appear to reflect the antirheumatic effect.

1. PHARMACOKINETICS OF ANTIMALARIALS

Cloroquine (CQ) and hydroxychloroquine (HCQ) are the only two 4-aminoquinoline derivatives used as antirheumatic drugs. The only difference between these drugs is the substitution of a hydroxyethyl group for an ethyl group on the tertiary aminonitrogen of the side chain of CQ.

Both AM are rapidly absorbed after oral administration and are quickly cleared from plasma. After efficient absorption in the gastrointestinal tract, CQ and HCQ disposition are characterized by extensive distribution in the tissues (8). The plasma half-life of CQ varies from 3.5 to 12 days with plateau plasma levels around 2 to 5 weeks (9). Similar findings have been reported for HCQ. Their extended half-lives result from the slow redistribution back into the blood from the large tissue repertories, including liver and muscle. Tissue concentrations of CQ and HCQ are much greater than plasma levels (10). However, tissue levels have been reported to be higher for CQ than HCQ which has been held to account for the differences in toxicity (11). The drug is

concentrated intracellularly, in acidic cytoplasmic vesicles. In vitro, CQ is concentrated approximately 7 to 20 fold intracellularly after 19 hours (vs extracelularly) (12). Although HCQ and CQ are concentrated within cells throughout the body, the important antirheumatic effects results from drug accumulation within the cells of the immune system.

In patients receiving CQ for malaria, therapeutic effects are quickly achieved at plasma levels of 0.05 μmol. In patients with arthritis who receive HCQ, 6 mk/kg/day, for at least 6 months, plasma level of approximately 0.9 μmol and a whole blood level of 3.8 μmol have been noted (13). This suggests that the antimalarial effects is not related to the antirheumatic effects of these drugs. In addition, CQ inhibits the haem polymerase, an enzyme which renders the haemoglobin breakdown products non-toxic to the parasite (14). This enzyme is involved in human haem processing, and could not appear relevant to the antirheumatic effects.

Randomized controlled trials of AM have shown that response to these second line agents is variable. About a quarter to one third of patients with RA are reported not to respond at all. Variation in plasma concentrations was proposed to be more closely related to clinical effect than dose. Thus, variability between subjects in pharmacokinetic parameters, leading to a large range of concentrations, is likely to cause variability in response. Tett et al. (15) showed a variable relationship between HCQ dose and steady-state blood concentrations in 43 patients with rheumatoid arthritis. A wide range of concentrations was observed in patients receiving the same dosage regimens. In addition, differences in the total clearance, calculated from single intravenous doses of HCQ in healthy volunteers have been shown by the same group (16). Furthermore, bioavailability studies have shown that the dose absorbed ranges from about 30 to 100% (17-18-). These data suggest that patients with high clearance and/or low bioavailability would achieve lower HCQ plasma concentrations than other patients and, if response is related to concentration,

may achieve insufficient concentration for a therapeutic effect. In fact, Tett et al (19) in a cross-sectional study demonstrated a relationship between HCQ concentration and effect in rheumatoid arthritis, with a better response in those patients with higher blood levels. In summary, HCQ disposition, including clearance and bioavailability of the oral dose form, varies between subjects causing variability in the dose concentration relationship. Variable concentrations are related to response in patients with RA, variable concentrations are likely to contribute to the reported variability in response to AM.

2. MECHANISM OF ACTION

The most likely relevant actions of AM are inhibition of enzyme activity and interference of cellular function in compartments in which there is an acid microinvorement, such as lysosomes, endosomes, and Golgi complex. These basic drug actions may subsequently affect pathways of inflammation and the immune cascade. Inhibition of pro-inflammatory enzymes including phospholipase A2 as well as decrease in the total prostaglandin production has been demonstrated (12). In addition to causing direct enzyme inhibition, AM stabilize lysosomal membranes, thereby inhibiting the release of lysosomal enzymes (6).

A crucial step in the regulation of the immune response is the processing of antigens by macrophages and the presentation of antigen-MHC protein complexes to CD4+ T cells. Processing in the macrophage involves the digestion of protein antigens into peptides in the lysosome and assembly of the peptides with MHC class II proteins (20). The antigenic peptide, generally 12 to 15 aminoacids in length, binds in a grove formed by the α and β chains of MHC class II molecules and is then presented to CD4+ T cells. AM may inhibit antigen processing and presentation in several ways. First, CQ and HCQ elevate the pH

within the lysosome and endosome. The elevated pH will retard the ability of peptides to form stable, compact α-β-peptide complexes (21). This effect will be more noticeable on peptides with lower affinity for MHC proteins. Second, AM may directly stabilize the α-Ii (the complex alfa chain-invariant chain) and β-Ii and retard their dissociation (22). Third, elevation of pH may influence the acidic hydrolases in the lysosome, leading to alteration of the digestion pattern of antigenic peptides and diminished degradation of Ii chain (23). Finally, elevation of pH in acidic vesicles may influence the recycling of α-β-peptide complexes from the cell surface, such that only high affinity α-β-peptide complexes may be returned to the cell surface (24). Additional effects of AM within the cell are: intercalation with DNA; inhibition of phospholipase A1 and C, inhibition of phagocytosis, inhibition of release of tumor necrosis, inhibition of superoxide production, decreased production of interleukin 1, and inhibition of antibody production (25-26).

CHAPTER 2

REVIEW OF THE LITERATURE: EFFICACY AND TOXICITY OF ANTIMALARIALS

The effectiveness of AM has been the subject of some controversy. The initial perception, decades ago, was that AM were the drug of choice for RA with an extremely good prognosis with respect to its use. As the first follow-up studies were published, it appeared that the outcome with respect to continuation of the drug use was not as impressive as the short term studies showed, with high rates of discontinuation due to lack of efficacy after the first 12 months, but with fewer discontinuations due to toxicity compared to other second line agents. In addition, one of the major problems in sifting data from all the different studies is the widespread variation in the clinical settings where the AM were tested and the disparity of doses used. Recent studies starting in the 1990's have again re-confirmed that long term effectiveness is not as good as was thought at the beginning of the AM era, but that they are probably the safest drugs of all second line agents including methotrexate.

One of the major problems in comparing differences between 2 drugs is the sample size required. Therefore, routine clinical trials are not suitable to evaluate either such differences or long-term effects. Another issue is the choice of measures to assess effectiveness. Effectiveness of a drug can be evaluated from several perspectives including clinical examination at the onset and at the end of therapy, laboratory and radiological tests (for rheumatoid arthritis), and evaluation of functional capacity, as well as rates of discontinuations over time.

1. AM AS ANTIRHEUMATIC DRUGS

The efficacy and toxicity of AM has been the subject of controversy. The initial perception, decades ago, was that both drugs might be equally effective and very safe. As the first major complications such as retinopathy were published, it appeared that toxicity was an important limiting factor for the use of AM in rheumatology (27). Recent studies, starting in the 1980's have reversed

this viewpoint, suggesting that AM are the safest drug among all second line agents.

The antirheumatic effect of AM was first described in 1894 by Payne who delivered a post-graduate lecture on lupus erythematosus in which he described the successful use of quinine for a rheumatic condition (28). However, the use of AM became more widespread after Page's report of success of quinacrine in patients with SLE and the control of the associated "rheumatoid arthritis" in two patients (29). This report subsequently influenced several groups to treat RA with AM. Although uncontrolled studies, all of them described similar responses to AM in RA at least in the short-term (< 6 months). In addition, several controlled clinical trials have been reported for CQ, some of them of short duration and some of longer duration. In all of them AM was clearly favored over placebo.

In the past two decades the spectrum of rheumatic diseases that has been reported to respond to AM has increased and includes dermatomyositis (30), palindromic rheumatism (31), psoriatic arthritis (32), and eosinophilic fasciitis (33).

2. AM IN RHEUMATOID ARTHRITIS

A. CHLOROQUINE

Shortly after Page's report of success with quinacrine in SLE several uncontrolled studies appeared suggesting that CQ was beneficial in 60 to 70 percent of RA patients and even remission of the disease could be achieved (34-35). Haydu (36) reported the findings in 28 patients treated with CQ for 6 months using 500 mg three times a week. Noticeable improvement was seen in 21 (75%) of these 28 patients. Lecapere et al. (37) treated 80 patients with doses up to 600 mg of CQ per day. No relapses were seen in those patients who received CQ in doses >400 mg/day. The time period was unfortunately

unspecified. In one of the largest uncontrolled studies, Bagnall et al. (34) reported his personal experience with 108 RA patients who received 250 mg/day of CQ. He found that a maximum response could be delayed for 6 to 12 months. Remission was noted in 39 cases, major response in 38 cases, minor or no improvement was seen in 36 patients (33%). Interestingly a higher response rate was seen in patients with shorter disease duration. Thus, 94% of the 36 "failures" had had their disease for more than three years. These uncontrolled studies were later confirmed by several short-term controlled trials (less than 6 months) (38-40) and long-term trials (> 6 months) (41-42). All short-term trials favored CQ over placebo, although few statistically significant differences were noted. However, some methodological problems are evident: small numbers of patients (8-69 patients), poor matching, and carry over effects (all 3 studies were crossover). Moreover, variations in the dosage used (200-600 mg day) make comparisons somewhat difficult.

Two controlled trials with duration of 1 and 2 years were reported in the sixties (41-42). Freedman and Steinberg reported their observations in 108 patients who received CQ (300-400 mg/day) over a 1 year period. Clinical improvement was noted in 80% of the CQ group in contrast to 30% of the placebo group. Again a higher improvement was seen in patients with disease duration of less than 1 year. Popert et al. (42) treated 61 patients either with CQ or placebo. Disease activity, grip strength, and erythrocyte sedimentation rate (ESR) were significantly better in patients with CQ. Again, changes were specially significant in patients with disease duration less than 2 years.

Some comparative studies have been also carried out. Klinefelter and Achurra (43-45). As might be expected no differences in the rates of response were seen in most of them mainly because of the small sample size. However, improvement with respect to their baseline was seen with all the drugs.

B. HYDROXYCHLOROQUINE

Fewer studies have been done with HCQ. In an open study Adams et al. (46) used up to 400 mg per day of HCQ and noted that 13 of 100 patients had complete remission and another 15 had more than 75 percent of improvement. One third had no response at all. Hamilton and Scott (47) in a controlled study found that 600 mg of HCQ was more effective than placebo. Mainland and Sutcliffe (48) reported the same results using 800 mg of HCQ.

The first two controlled clinical trials to compare HCQ 400 mg/day with placebo were reported recently. These studies are the only two controlled trials comparing HCQ with placebo at the currently used dose. Both studies concluded that HCQ was superior to placebo. Clark et al. (49) in a 24-week randomized controlled trial reported that HCQ showed a clinically and statistically significant improvement over placebo in joint score, pain, grip strength, patient's global assessment and physician's global assessment. Side effects were mild and none of them lead to discontinuation of the HCQ. However, the number of patients who developed side effects were high in both groups (52 (83%) in HCQ and 39 (67%) in the placebo group. Of interest, was that both groups showed clinical and statistical improvement during the course of the study. Thus, a large placebo effect was seen, however, a statistically significant differences was noted in favor of HCQ. The HERA study showed similar results (50), joint index, pain index, and the physical functional index showed a significant differences in favor of HCQ.

C. LONG-TERM STUDIES

There are few studies evaluating the long-term effectiveness of AM. Ritcher et al. (2) in a retrospective study of 134 patients compared the treatment terminations between gold salts and AM. They concluded that patients taking AM

compounds tended to terminate treatment sooner that those who received gold. The frequency of treatment termination due to side effects was less than 10% at 50 months at which time the total termination rate was 71%. In contrast the treatment terminations of gold salts for all causes was less than 50% at 60 months. Although the authors included patients with CQ or HCQ they analyzed them as a single group.

Husain and Runge (51) evaluated the rates of discontinuation at 24 months for HCQ (400 mg/day) in patients with RA and compared with gold, levamisole, and D-penicillamine. HCQ had the lowest incidence of discontinuation for any reason (17 % at 6 months and 30 % at 15 months).

Wolfe et al. (3) during a continuous 14-year observation period recorded prospectively clinical data on 671 patients (269 on HCQ) for a total of 1017 consecutive starts of 5 antirheumatic agents. The median treatment termination time for all causes with HCQ was 2.01 years (95% CI 1.72-2.71), being the second best after methotrexate. Six percent of the HCQ discontinuations were due to lack of efficacy. The main adverse reactions associated with discontinuation of AM therapy were gastrointestinal (36%), rash (26%), and ophthalmologic (18%). CQ was not used in this study.

Wijnands et al. (4) in a prospective study evaluated the long-term effectiveness of 4 anti-rheumatic drugs over a period of 42 months. HCQ had the lowest rate of discontinuation due to toxicity (10%). Of interest, these discontinuations occurred during the first year of therapy with no further treatment terminations due to toxicity. On the other hand, the rate of discontinuation due to lack of efficacy was the highest for HCQ (51%). Forty-four percent of them occurred during the first 1 year and reached 61% at 2 years. Again CQ was not used in this study.

Pincus et al. (52) evaluated the probability of continuation of 1077 courses of second line agents taken by 532 patients with rheumatoid arthritis treated in 7 rheumatology private clinics. Only 50% of the HCQ courses were continued at 20

months. Methotrexate and prednisone were the only drugs continued by more than 50% of patients after 60 months. CQ was not used in this study.

Suarez-Almazor et al. (5) evaluated the long-term effectiveness of second line agents in an inception cohort of patients with RA. They reported that at 48 months around 40% of the patients with AM had discontinued the drug. Inefficacy and toxicity accounted for 35% and 24% respectively. Again CQ and HCQ were considered as a single group.

Finally, Hawley and Wolfe (53) evaluated the validity and generalizability of the results from controlled clinical trials and observational studies of second line agents in RA in 122 studies. Although 10 arms for HCQ and 6 treatment arms for CQ were identified, the authors analyzed AM as a single group. They concluded that short-term studies were not representative of long-term results.

3. AM IN SYSTEMIC LUPUS ERYTHEMATOSUS:

The first line treatment of SLE has consisted of topical steroids, non-steroidal antiinflammatory drugs and AM.

Early studies showed that AM were effective in the control of skin manifestations of SLE and also noted relapses upon discontinuation of the drug in up to 80% of cases, usually within 3 to 6 months (55-55). Moreover AM have been reported to improve other aspects of mild to moderate SLE (56-57).

Although there is clinical consensus on the efficacy of AM for the control of some of the most common manifestations such as arthritis, rash, serositis, and the debilitating fatigue that accompany SLE, until now there have been no controlled clinical trials evaluating the efficacy of these agents in SLE. However, 2 studies have evaluated the effect of AM discontinuation in patients who achieved control of the disease with AM.

Rudnicki et al. (57) in a retrospective study evaluated 43 patients with SLE who developed macular lesions while receiving a variety of AM. The authors

matched each eligible year on AM with a subsequent year after discontinuation of the drug. These 43 patients had 76 years that could be matched (76 years on and 76 years off of AM). Thirty-four patients had received CQ. High dose of CQ (500 mg/day) was given in 20 cases and this dose was associated with significantly fewer constitutional symptoms (fever, fatigue, weight loss) and skin rashes. The author also noted that the use of AM was associated with a significant reduction in the frequency of disease flare-ups.

This was the first controlled evaluation of AM in SLE. Because of the design of the study, the years on AM were earlier than the years off AM for every patient. To the extent that the disease activity of SLE may diminish with time, the study design would bias the results. Moreover, the CQ doses were often higher that those generally used today.

The Canadian HCQ study group conducted a 6 month randomized discontinuation trial (58), in forty seven patients with quiescent SLE that were receiving HCQ in an average dose of 272 mg/day and had received the drug for a mean of 37 months prior to the study. Twenty five were randomized to continue their same dose of HCQ and 22 were randomized to receive placebo. The primary outcome of the study was the time to develop a clinical flare. They found that patients on placebo had significantly more flares and also the time to a flare up was shorter. Patients taking placebo were 2.5 times more likely to flare (CI 95 % 1.08 to 5.58) than those continuing to take HCQ.

The preliminary results of an ongoing 48-week randomized clinical trial of HCQ for lupus arthritis suggested a significant improvement in patient-reported severity of joint pain, satisfaction with functional ability, and self- report of the number of painful and swollen joints (59). However, objective physician-determined measures showed no significant differences between the groups.

Although dissenting opinions exist, AM have generally been considered to be corticosteroid sparing in both discoid lupus and SLE (60). However these observations have been noted in uncontrolled studies.

4. AM IN OTHER RHEUMATIC DISEASES.

Palindromic rheumatism is a disorder characterized by recurrent, afebrile attacks of pain, swelling and redness in or around one or occasionally more joints with episodes of complete remission in between attacks. The disease may be disabling, and one third to one half of the patients may progress to classical rheumatoid arthritis. Several authors have reported the benefical effect of AM in palindromic rheumatism in a small number of patients (31, 61, 62). Youssef et al. (31) reported the efficacy of CQ in 51 patients with palindromic rheumatism. Eighty percent of the patients experienced marked improvement with 77.5% reduction in frequency and 63% reduction in duration of attacks. Only 4 patients received HCQ.

5. CHLOROQUINE VS HYDROXYCHLOROQUINE

Unfortunately there is only one study that made comparisons between CQ and HCQ in the same setting. In 1958 Scherbel and Scuchter (63) reported the results of 45 patients with RA who were treated with HCQ (200 to 600 mg daily) or CQ (250-500 mg daily). Clinical status after 18 months of therapy showed that of the 26 patients who were receiving HCQ, 15 (58%) were "asymptomatic", 5 (19%) patients had "significant improvement", and 6 (23%) patients had "unsatisfactory response". Of this latter group three (11%) stopped the drug due to side effects and 3 (11%) were considered as a drug failures after 6 to 9 months of therapy.

Of 25 who received CQ, 9 (36%) were "asymptomatic", 8 (32%) had "moderate improvement", and 8 (32%) had "unsatisfactory results". Six (24%) had side effects and 2 (8%) were "drug failures". A subsequent report (16) from the same centre with 106 patients, (60 with HCQ and 40 with CQ) showed similar results. The authors concluded that in equal dosage HCQ was one half to

two thirds as potent as CQ (600 mg of HCQ were as effective as 250 mg CQ), while the frequency of drug reactions was one half that of CQ.

The main difficulty in demonstrating what may be clinically important differences in the efficacy and toxicity between two antirheumatic drugs appears to be the sample size required. Metaanalysis has the unique advantage of substantially increasing the sample size because it combines data from multiple studies. Felson et al. (64) using this technique found that CQ was more effective than HCQ at the conventional dosage (250 mg/day of CQ and 400 mg/day of HCQ). No differences in toxicity were found. However, this study included only controlled clinical trials and thus only the short-term effects are evaluated.

Once it was established that AM could cause loss of vision, safety became the paramount issue and perhaps the major limiting factor for AM use (65). Ocular toxicity and especially retinal toxicity are supposed to be where the main difference between CQ and HCQ exists.

Finbloom et al. (66) reviewed the records of 110 patients who had received greater than 100 g of CQ and/or HCQ over a period of 15 years to compare the development of retinal toxicity between these two drugs. Only 7 cases (6%) of retinopathy were identified (3 RA, 2 SLE, 2 discoid lupus). Six of these took CQ and 1 had both AM (at different times), CQ being the predominant drug. Of note, 4 of these 7 patients were taking 2 or 3 pill/day at various times during the course of their treatment. The authors concluded that CQ could be more toxic than HCQ. However, data derived from patients receiving an excessive daily dose of AM cannot be extended to the currently accepted daily dose. Esterbrook (67) reported his observations on examination of 2,000 patients treated with CQ and HCQ. He found 75 cases of retinopathy (72 from CQ, 3 from HCQ).

Finally, in a very recent report, Landewe et al (68) reported that AM induce a decrease in creatinine clearance. After adjusting for several confounders the type of AM had a significant correlation with the decrease. CQ

resulted in a mean decrease of creatinine clearance of 11.3% while HCQ had 1.7%. Although these results may not be clinically relevant, they are of interest first, because AM have been considered as a non-nephrotoxic drugs and second because this nephrotoxicity is different for each AM. It supports the general belief that CQ and HCQ have a different toxicity profile.

6. AM PATTERNS OF PRESCRIPTION

Bellamy and Brooks (69) evaluated the prescribing practices for CQ and HCQ between rheumatologists in Canada and Australia. Eighty percent of the Australians preferred HCQ compared with only 55% of Canadians. Eleven percent used both CQ and HCQ. Seventy-eight percent of rheumatologists reported that between 1-50% of patients refused AM therapy, most because of concern regarding ocular toxicity. Although the survey did not evaluate the reasons for the preferences of either AM, the authors speculated that ocular toxicity was the most important factor to be considered in the AM selections.

CHAPTER 3

RATIONALE AND OBJECTIVES OF THE STUDY

1. LIMITATIONS OF PREVIOUS STUDIES

Several methodological issues have to be considered in analyzing long term effectiveness of any drug. In rheumatic diseases, the difficulties are even greater because of the fluctuating nature of their signs and symptoms which may bias the selection and follow-up of patients. Most of the studies evaluating long-term effectiveness of AM have considered both drugs in a single group. Moreover, in some places such as United States of America CQ is not longer recommended. Thus HCQ appears to be preferred on grounds of safety. There are only two studies comparing CQ and HCQ. The published differences are contradictory, these differences can be attributed, at least partially to differences in design and methodological biases.

A. TYPE OF STUDY

Studies may differ due to differences in the design, selection of patients, and follow up. Effectiveness studies are not the exception. There are two types of studies to evaluate effectiveness: experimental (randomized controlled trials) and observational studies.

1. *Randomized controlled trials (RCT):*

There is no doubt that RCT are the gold standard to evaluate differences between two drugs. This design would include patients who will receive the drug(s) of interest once they have been defined. They are randomized to receive either drug. Random assignment implies that each individual has the same chance of receiving each of the possible treatments and that the probability that a given subject will receive a particular allocation is independent of the probability that any other subject will receive the same treatment assignment.

Thus, the potential for bias in allocation to study groups is removed, and investigators can be confident that observed differences are not due to selection of particular patients to receive a given therapy. Whether the subgroup of patients under experimental conditions are representative of the entire population will not influence validity. It may, however, affect the ability to generalize the results. This is perhaps the only major limitation, besides the costs.

There is not a single RCT comparing CQ and HCQ and it is unlikely that this will be done, primarily because of the sample size required and the associated high costs of carrying out this kind of study.

2. *Observational studies*

There are two basic types of observational analytic studies: the case control and the cohort study.

In a case control study, a case group or series of patients who have a disease of interest and a control group of individuals without the disease are selected for investigation, and the proportions with the exposure of interest in each group are compared.

In contrast, in a cohort study, subjects are classified on the basis of the presence or absence of exposure to a particular factor and then followed to determine the development of the outcome of interest.

The choice of which type of design to use to study a particular exposure-outcome relationship depends on the nature of the outcome of interest, the type of exposure, and the available resources. For example, the case-control design is particularly efficient for investigation of a relatively rare outcome since it selects a group of individuals who have already developed the outcome. Conversely, cohort studies are best suited to investigations of relatively common

outcomes that will accrue in sufficiently large numbers over a reasonably short period of follow-up.

- There is not a single observational study comparing CQ and HCQ.

B. Duration of follow-up

It is clear that the results of a 6 months study can not be compared to results of a 5 year study. The majority of controlled clinical trials of AM are short term (less than 1 year) (38-42, 49, 50). Studies comparing long-term effectiveness between AM are not available in the literature., as most of them have considered AM as a single group. All short term studies have found high rates of efficacy with low rates of toxicity (38-42, 49-50). However, long-term studies have reported high rates of inefficacy although with low rates of toxicity, at least in RA. (3-5, 52).

C. Sample size and power

The sample size of the study may be a major determinant of different results between studies. As the sample size increases, so does the probability of detecting real differences at a statistically significant level. In addition, the power of the study increases with the sample size. Thus, the lack of differences between two drugs may be only a reflection of greater sample size required to find such a difference if this really exists.

Most of the RCT have compared each AM with placebo. However, comparisons between CQ and HCQ have not been done. Using the meta-analysis technique Felson et al. reported that CQ was more efficacious than HCQ with no differences with respect to toxicity. This results contrast with those reported in observational studies with smaller samples (64).

C. Choice of outcome measures

Of major concern is the potential bias in the measurement of the outcome variables when evaluation is not blinded. With respect to toxicity or efficacy in experimental studies (RCT) it is known that toxicity is overestimated. In addition in most studies an a priori definition is used in order to establish associated drug-side effects. On the other hand, in observational studies side effects might be underestimated since only those side effects leading to discontinuation of the medication tend to be reported in the medical record (i.e. the clinically relevant issues).

D. Adjustment for confounders

The influence of confounding variables has rarely been taken into account in most studies. Moreover, similar studies often do not adjust for the same confounders and the final result may differ for this sole reason.

2. OBJECTIVES AND HYPOTHESES

The main objective of this study was to evaluate the long-term effectiveness of AM in general in patients with rheumatic diseases, and compare long-term effectiveness between CQ and HCQ. For this purpose, the first step was the selection of the cohort. A cohort of patients who received AM from 1985 to 1993 for any rheumatic disorder was retrospectively selected. The specific objectives of the study were both descriptive and analytic.

2.1 DESCRIPTIVE OBJECTIVES

-To describe the use of antimalarials in rheumatic diseases.

-To describe the reasons of discontinuation of antimalarial therapy

-To compare the long-term effectiveness between CQ and HCQ.

2.2 ANALYTIC OBJECTIVES

-To examine the relationship between demographic factors, type of antimalarial therapy (CQ vs. HCQ) and the outcome of antimalarial therapy.

-To quantify the risks of demographic variables in relation to the different outcomes of antimalarial therapy (discontinuations due to toxicity, inefficacy, and overall).

2.3 HYPOTHESES

The following working hypotheses were established a priori:

- Long-term effectiveness (efficacy and toxicity) between chloroquine and hydroxychloroquine in rheumatic diseases is different.

- Demographic factors, type of antimalarial (CQ Vs. HCQ), physician, rank selection, combination, as well as disease factors are independently associated with the causes of discontinuation of antimalarial therapy.

3. RELEVANCE OF THIS STUDY

Although CQ and HCQ have been used for the treatment of rheumatic diseases for more than 30 years they have been considered as a single entity in all studies which have evaluated the long-term effectiveness of second line

drugs in RA. There are differences in the patterns of prescription for AM. Furthermore, these preferences also have economic implications since there are considerable differences in the price between AM. These preferences should be based on the best efficacy/toxicity ratio in the long-term; until now a study evaluating these long-term effects has not been done.

The proposed study will be the first to compare the long-term effectiveness between CQ and HCQ.

Although the best method to compare two drugs is a controlled clinical trial, several limitations such as sample size, costs, and time make this impractical.

There is indirect evidence from observational studies which suggests that potential differences between CQ and HCQ are small at least in the short-term (36, 64-65), therefore the required sample size to reach statistical significance would be large. In addition, a controlled clinical trial is much more expensive than a retrospective cohort study, especially if we take into account that the end points are long-term effects. Thus, in our centre it would take eight years to accrue the sample size comparable to that proposed in this study plus an additional year of follow-up. Thus a controlled clinical trial would not be as feasible as the approach proposed here.

Randomized controlled trials (RCT) are considered the best design to compare the efficacy of two drugs. However, they are not very well suited to evaluate the community long-term effectiveness of interventions. They have several limitations which relate to the external validity of the results (generalizability) and feasibility issues (sample size, length of follow-up, costs). Moreover keeping the blindness of RCT for long periods of time results in difficulties as well as affecting the patient's compliance.

CHAPTER 4

PATIENTS AND METHODS

1. DESIGN OF THE STUDY

The study protocol was based on a retrospective cohort design with a follow-up up to eight years. A cohort of patients who received AM therapy between January, 1985 and December, 1993 was identified retrospectively. Medical records were then evaluated during the period from January 1994 to January 1995.

2. SELECTION OF THE STUDY COHORT

In order to accomplish the objectives of the study, the first step was to assemble a cohort of patients who had received AM therapy for any rheumatic disease, from 1985 to 1993. To avoid erroneous diagnoses and therefore unnecessary therapy with AM, it was decided that only AM prescribed by a rheumatologist would be considered for inclusion in the cohort. Nine rheumatologists had a medical practice in the city of Edmonton at the beginning of the study (January 1994). Of these, five were in practice in 1985 and the other 4 started practices in subsequent years (1986, 1988, 1989, 1990). Medical records of rheumatologists practicing only in tertiary centres were included in the study (seven rheumatologists). Internal medicine is the main practice of one of the rheumatologists not included in the study. The other one started practice in 1991. All rheumatologists agreed to participate in the study and allowed a review of their medical records.

The selection of the cohort was conducted in two steps:

1. Initial selection of potential cases from rheumatologists' records
2. Definitive selection of patients complying with specific criteria after review of medical records.

2.1 INITIAL SELECTION OF POTENTIAL CASES

Medical records of all patients seen from January 1 1985 through December 31 1993 by the seven rheumatologists included in the study were reviewed in order to select potential cases for the cohort. At the time of the study none of the rheumatologists had an updated computerized database of patients including diagnoses or therapy. For this reason the selection of patient records had to be performed manually. Thus, all medical records had to be reviewed in order to select those patients who received AM therapy.

Five rheumatologists had their practices at the University of Alberta Hospital (Rheumatic Disease Unit). All of them filed medical records by year. Thus, records of those patients seen in 1985 are filed together. If a patient was seen again in 1988, then the medical record is removed from the 1985 group and filled in 1988. Therefore, we started reviewing the oldest year (1985) and leaving the last year (1993) to be reviewed during the last months of the study to avoid missing patients. The other two rheumatologists had their practices at the Royal Alexandra Hospital. They filed their medical records in two groups: those seen during the current year, and those seen from the previous years (e.g., those seen currently during 1996 and the rest). Therefore, we reviewed first those seen previous to the last year (1994) and leaving the last year until the end.

In Edmonton all rheumatologic patients seen by the rheumatologists are referred by the family physicians. A previous study (70) evaluating the outcome of rheumatoid arthritis showed that most the patients seen by the family physician who complained of arthritis or related conditions are sent to a rheumatologist. Therefore the sample to be evaluated in this study does not have the referral bias usually seen in other tertiary care centres, where the most severe patients are those who reach the tertiary care centre.

2.2 REVIEW OF MEDICAL CHARTS

All the medical records selected following the procedures just described above were reviewed by a rheumatologist in order to select patients for the cohort. The following inclusion criteria were used at this point:

1. Diagnosis of any rheumatic disorder confirmed by a rheumatologist. Thus no diagnostic criteria (research criteria) were used to define a rheumatic disorder.
2. Onset of AM therapy between January, 1985 to December, 1993.

2.3 DEFINITE INCLUSION IN THE COHORT

Patients who received AM prior to 1985 were not included in the cohort. Thus, a patient who received two cycles of AM therapy and one of them was in 1985 in the other beforehand, e.g., in 1982 was not included. This was to avoid bias in the selection of patients. Medical records which had missing information on AM therapy were not included (e.g., date of starting or stopping AM therapy). Moreover, patients seen only once were also excluded.

3. EXTRACTION OF MEDICAL CHART INFORMATION

Medical information from the rheumatologist records was extracted and coded by the author using structured forms. Information was obtained on demographic data, diagnoses, therapies prior to the use of AM, date of starting AM therapy, date of stopping AM therapy, reason of discontinuation (according to the treating rheumatologist), dose and changes during the follow-up (Appendix 1).

4. STUDY VARIABLES

Variables used in the study were numerically coded. The variable of primary interest was the outcome of antimalarial therapy. Thus, the antimalarial status at the last note available in the medical chart which could be grouped in at least one of the following: a) still on therapy, b) discontinued because of toxicity, c) discontinued because of inefficacy, d) discontinued for other reasons not related to ones mentioned previously. All of these outcomes were obtained from the rheumatologist's note. Other important data such disease type, date of diagnosis, therapy prior to the onset of AM were also recorded. Demographic data such as gender, age, address, and telephone number were collected. Most of these variables have been suggested to be related with effectiveness of antirheumatic therapy. Other variables of interest were those related to side effects especially ocular side effects, which have been suggested to be different between CQ and HCQ.

Some authors have shown that some physician characteristics as well as some patient characteristics are relevant to the selection of a particular second line drug. These include physician sociodemographic features, type of practice and reimbursement.

All the seven rheumatologists in the study have practiced in Edmonton for several years, and the four younger ones trained in Rheumatology at the University of Alberta. The similar training and geographical proximity should partially provide comparable educational opportunities. Furthermore, for most of the period under the study, all of the rheumatologists had similar reimbursement schemes (fee-for service, universal single payer system).

Other variables of paramount importance are clinical status of the disease at the onset of therapy (disease activity). Unfortunately, from the medical record it is impossible to obtain this information since rheumatologists usually do not collect this information in a standard manner.

5. STATISTICAL METHODS

5.1 BIVARIATE ANALYSES

The initial exploratory analyses were conducted using the following statistical tests (71-72):

a. Chi-square tests were used to compare differences between proportions. A Fisher exact test was used in 2 by 2 tables when one of the cells had a expected number less than five.

b. *t*-tests to compare differences in means between 2 groups. An *F* test was used to test for equality of variances. If the *F* test was significant ($\leq$ 0.05) a *t*-test based on separate variances estimates was conducted. Otherwise, a pooled variance *t*-test was used.

c. Kaplan-Meier survival methods were used to study the probability of discontinuation of AM therapy (73). All patients who did not reach an end point (discontinuation of AM therapy) were considered as censored. In addition, all those who discontinued for whatever reason other than the end point (discontinuation due to toxicity or discontinuation due to inefficacy) were also considered as censored. None of these causes were assumed to be related to the main end points. It is possible that some patients discontinued for two reasons (toxicity and inefficacy) if this was stated as that in the medical record, then it will be considered as an end point in each of the two groups (toxicity and inefficacy).

5.2 MULTIVARIATE ANALYSES

The following statistical method was used:

a. Cox-regression model

Cox regression model was used for the following purposes:

a) To evaluate the effect of independent variables (covariates) on the dependent variable taking into account censored (cases for which the event of interest has not yet occurred) observations.

When the cumulative survival function, that is, the proportion of cases "surviving" at a particular point in time is the dependent variable the Cox-regression model can be written:

$$h(t) = [\, h_0(t) \,] e^{(\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots + \beta_p X_p)}$$

where : X_1 to X_p are the covariates and β_1 to β_p are the coefficients respectively.

$h_0(t)$ = baseline hazard function

Thus, the proportion surviving to time ***t*** depends on the baseline hazard function [which is independent of the covariate(s), it depends only on time], as well as, ***e*** depends not on time but on the value of the covariate and on the value of the regression coefficient β.

Categorical variables were modeled by creating a set of dummy variables, with the number of dummy variables needed to represent a categorical variable equal to one less than the original number of categories. The first category was used as the reference category for each of the other categories.

For dichotomous variables such as gender, two sequential numbers were used for coding (0 for men and 1 for women), and the larger of the two indicated the characteristic, therefore e^{β} is the ratio of the estimated hazard for a case with the characteristic to that for a case without the characteristic.

Models were built using four different methods:

a) Each covariate was entered as a single variable in order to test if that single covariate was a significant predictor.

b) Forced entry, where covariates thought to be relevant by the investigator were kept in the model, regardless their level of significance.

c) Best model, where variables were selected according to their relevance in the model (using the likelihood ratio and the Wald statistic).

d) Best model with interactions, where interactions between the covariates were tested.

CHAPTER 5

RESULTS 1

CHARACTERISTICS OF THE COHORT

1. INITIAL SELECTION OF THE COHORT

Seven rheumatologist were practicing in the two tertiary centres included in the study. All but one had been in practice before 1985. After reviewing around 52,000 medical records, 1042 eligible cases were identified. From these, 940 (90%) had usable information and they represent the cohort.

1.1 DEMOGRAPHIC CHARACTERISTICS

Nine hundred and forty patients were included in the cohort. Demographic characteristics are shown in Table 5.1. The mean age at the onset of AM therapy was 47 years. Patients who received HCQ were significantly older than patients who received CQ. Rheumatoid arthritis accounted for almost two thirds of the AM prescriptions. Moreover, CQ was the main AM in all disease groups. AM were selected as a the first second line therapy seventy percent of the cases with no significant differences between CQ and HCQ. Thus, antimalarials were used early among other second line agents available for the treatment of rheumatic diseases. As expected, statistically significant differences were seen in all demographic variables among diseases groups (Table 5.2). CQ was the most prescribed AM in all disease groups. AM combinations with other second line drugs were seen almost exclusively in RA.

A. GENDER

Females were the predominant gender in general, in accordance with the prevalence of rheumatic diseases. This was seen in all disease groups (Table 5.1 and Table 5.2).

B. DISEASE DURATION

Disease duration was calculated from the medical record according to the rheumatologists' note with respect to the disease onset. In 68 patients (7%) it was not possible to calculate disease duration because disease onset was not stated in the chart. Overall, almost two thirds of the patients receiving AM had less than 2 years of disease duration. However, when disease duration was compared among diseases groups all were statistically significant, with RA having the longest duration (Table 5.2). Early initiation of second line therapy may have a critical role in the treatment of rheumatic diseases, at least for RA. It is believed that patients initiating treatment at earlier stages may respond better to treatment. Table 5.3 shows the proportion of patients with disease duration of less than 2 years among the different disease groups and by type of AM. No differences with respect to disease duration were seen between CQ and HCQ

C. ANTIMALARIAL THERAPY

Overall, CQ accounted for 57% of the AM prescriptions. This drug was the main AM in all disease groups. RA was the only disease group which received both drugs in similar proportions (51% and 49% for CQ and HCQ respectively) (Table 5.2).

D. RANK SELECTION

Table 5.1 summarizes the order in which the different AM were chosen for therapy. Overall, more than 70% of the cases received AM as the first second line drug for the treatment of the underlying disease. Furthermore, when comparisons among the disease groups were made SLE and PA received the

AM therapy almost exclusively as the first choice (95% and 98% respectively). However, for RA AM were the first choice in almost two thirds of the patients.

D. COMBINATIONS

One hundred and seventy-four patients received AM in combination with other drugs. There were differences between CQ and HCQ with respect to combinations, with HCQ having a higher rate of combination. Gold compounds were the main second line drug in such combinations and it was seen almost exclusively in RA patients.

Table 5.1. Demographic data

Feature	AM n(%)	CQ n(%)	HCQ n(%)	p value (*)
Gender				
Female	719 (77)	405 (75)	314 (79)	NS
Male	221 (23)	136 (25)	85 (21)	NS
Disease duration (**)				
mean in years (±SD)	4.1 (6.6)	4.0 (6.5)	4.2 (6.8)	NS
Age mean (±SD) **(**)**	47 (15.5)	45.3 (14.8)	49.2 (16.2)	<0.0001
Drug				
CQ	541 (57)	---	---	
HCQ	399 (43)	---	---	
Disease				
RA	557 (59)	287 (53)	270 (68)	<0.0001
SLE	178 (19)	113 (21)	65 (16)	NS
PA	128 (14)	91 (17)	37 (9)	<0.001
Other	77 (8)	50 (9)	27 (7)	NS
Rank				
First	676 (72)	402 (74)	274 (69)	<0.05
Other	264 (28)	139 (26)	125 (31)	<0.05
Combination	174 (19)	85 (16)	89 (22)	<0.01

(*) CQ vs. HCQ (**) At the onset of AM therapy NS= not significant

Table 5.2 Demographic data by disease group.

Feature	RA n(%)	SLE n(%)	PA n(%)	OTHER n(%)	p value (*)
Gender					
Female	426 (77)	154 (86)	85 (66)	54 (70)	<0.001
Male	131 (23)	24 (14)	43 (34)	23 (30)	
Disease duration (**)					
mean in years (±SD)	4.6 (7.4)	3.2 (4.7)	3.2 (5.8)	4.3 (5.4)	<0.04
Age mean (±SD) **(**)**	52 (15)	36 (13)	42 (12)	41 (15)	<0.001
Drug					
CQ	287 (51)	113 (63)	91 (71)	50 (65)	<0.001
HCQ	270 (49)	65 (37)	37 (29)	27 (35)	
Rheumatoid factor					
negative	151 (27)	-----	42 (33)	24 (31)	<0.001
positive	328 (59)		40 (31)	11 (14)	
unknown	78 (14)		46 (36)	42 (55)	
Rank					
First	327 (59)	169 (95)	126 (98)	54 (70)	<0.001
Other	230 (41)	9 (5)	2 (2)	23 (30)	
Combination	151 (27)	9 (5)	1 (3)	10 (13)	<0.001

(*) CQ vs. HCQ (**) At the onset of AM therapy NS= not significant

Table 5.3 Disease duration at the onset of antimalarial therapy among diseases.

Disease	AM n(%)	CQ n(%)	HCQ n(%)	p value (*)
RA (n=557)				
< 2 years	310 (56)	155 (54)	155 (57)	NS
> 2 years	212 (38)	107 (37)	105 (39)	
unknown	35 (6)	25 (9)	10 (4)	
SLE (n=178)				
< 2 years	104 (58)	65 (58)	39 (60)	NS
> 2 years	55 (31)	34 (30)	21 (32)	
unknown	19 (11)	14 (12)	5 (8)	
PA (n=128)				
< 2 years	83 (65)	60 (66)	23 (62)	NS
> 2 years	40 (31)	28 (31)	12 (32)	
unknown	5 (4)	3 (3)	2 (5)	
OTHER (n=77)				
< 2 years	35 (46)	23 (55)	12 (46)	NS
> 2 years	33 (43)	19 (45)	14 (54)	

NS= not significant

CHAPTER 6

RESULTS 2

ANTIMALARIAL

DISCONTINUATIONS

1. ANTIMALARIAL DISCONTINUATIONS

From the 940 cases, sixty (6%) of the patients received more than one course of AM therapy. In addition, six percent of the cases received both AM at different times. However, for the purposes of this study only the first cycle as well as the first AM were considered in the analysis.

Table 6.1 shows the causes of discontinuation for AM in general. Overall, 468 patients (50%) were still on AM therapy at the time of data collection. Toxicity was the main cause of discontinuation for CQ and this reached a statistically significant difference when compared to HCQ. In contrast, inefficacy was the main cause of discontinuation for HCQ, however this was not statistically significant when compared to CQ. Other various reasons accounted for 13% and 18% for HCQ and CQ respectively ($p<0.01$). From these, discontinuations by the patient and pregnancy were the only which reached a statistically significant difference. Overall, in 2% of the cases the reason of discontinuation was unknown and they were considered as a missing values; these rates where similar between CQ and HCQ. Using the missing values either as a discontinuations due to toxicity or inefficacy the (sensitivity analysis) results did not change. In general, the overall, as well as each one of the reasons for discontinuation of AM therapy were similar between CQ and HCQ, although some reached a statistically significant difference.

2. SURVIVAL TIME ANALYSIS

Survival time analysis was conducted using the Kaplan-Meier product limit method to calculate the proportion of patients still receiving any AM at different points in time (Figure 6.1). Overall 50% of the discontinuations occurred in the first 5 years then a plateau was observed. Around 30% of the

cases were still on AM therapy at 120 months. This rate differs from the crude rate observed in table 6.1 (50% were still on AM therapy at the time of data collection) because time was not accounted in the crude rate. Figures 6.2 and 6.3 shows the survival for toxicity and inefficacy respectively. Overall, after adjusting for time 50% and 40% of the patients discontinued at the end of the study because of toxicity and inefficacy respectively.

Survival curves were calculated for each drug in terms of the following causes of discontinuations: a) all causes, b) toxicity, and c) inefficacy (Figures 6.4 to 6.6). The p values is the result of testing for equal rates of drug continuation (equal survival) between the 2 curves being tested using the log rank test statistic. The curves seen in Figure 6.4 are very similar to those observed in Figure 6.1. Around 30% of the patients were still on therapy at 120 months with no difference between CQ and HCQ. This similarity is seen across all different points in time. However, when survival curves were estimated for discontinuations due to toxicity (all other causes of discontinuation and no discontinuation were considered as censored) a trend for more discontinuations in patients who received CQ than those who received HCQ was seen. However, this difference was not statistically significant (Figure 6.5). In addition, during the first 30 months discontinuations between both drugs are very similar, then no discontinuations are seen in patients with HCQ while patients on CQ were still discontinuing because of toxicity. Unlike to all causes of discontinuations and toxicity; discontinuations due to inefficacy were statistically significant between CQ and HCQ (Figure 6.6). Patients who received CQ discontinued less often as a consequence of inefficacy than patients who received HCQ. This difference starts to be noticeable after about one year and continus until 70 months then a plateau is reached in both drugs.

The censored data used in all the estimations mentioned previously were all discontinuations other than the event of interest. In addition, all

censored data were considered independent among themselves as well as the end points. Thus, when toxicity was considered the end point inefficacy was considered as censoring and viceverse. However, it is possible that in some patients both events occurred at the same time, but this information was not available in the medical record. Therefore, only the reason of discontinuation according to the treating rheumatologist was considered the main cause of discontinuation. Table 6.2 shows the mean times of discontinuation for AM in general and for each drug. Only the mean time of discontinuation due to inefficacy reached a statistically significant difference.

A. DISEASE GROUPS

Statistically significant differences in drug continuation rates (survival) were seen among diseases with respect to any cause of discontinuation ($p<0.001$); with SLE having the highest continuation rate and RA the lowest (Figure 6.7). There were no statistically significant differences with respect to continuation rates due to toxicity among diseases ($p<0.10$) (Figure 6.8). This suggest that AM toxicity is not related to disease type. However, there was a statistically significant difference in continuation rates due to inefficacy ($p<0.0001$), with SLE having the highest continuation rate and RA the lowest (Figure 6.9). Table 6.3 shows the mean times of discontinuation for each disease with respect to overall, toxicity, and inefficacy.

Figures 6.10 to 6.18 show the discontinuation rates for all causes of discontinuation, discontinuations due to toxicity, and discontinuations due to inefficacy in each disease group. No statistical significant differences between CQ and HCQ were seen in any disease group with respect to all causes of discontinuation. In all diseases groups 50% of all discontinuations occurred around the first 20 months (Figures 6.10, 6.13, 6.16). Rates of discontinuation due to toxicity were higher for HCQ in PA and this was statistically significant.

Here, 30% of the CQ discontinuations occurred at 20 months while the same rate occurred at 55 months in the HCQ group (Figure 6.17). In contrast, CQ had a trend for higher rates of discontinuation due to toxicity in RA and SLE, but these were not statistically significant (Figure 6.11 and 6.14). Finally, continuation rates for inefficacy were statistically significant only in rheumatoid arthritis; with CQ having a higher continuation rate. This difference started to be apparent after 10 months (Figure 6.12). For all causes of discontinuation and for discontinuations due to inefficacy, the patterns for CQ compared HCQ across disease type are either not statistically significant or qualitatively similar. Only for discontinuations due to toxicity in PA (Figure 6.17) is the pattern different. This suggests the possibility of a disease-AM interaction in the case of discontinuation due to toxicity.

B. RHEUMATOLOGIST

When survival rates were plotted for the different rheumatologists, statistically significant differences were seen in the overall and toxicity rates ($p<0.03$ and $p<0.05$ respectively) (Figures 6.19 to 6.21). These suggests that rheumatologists might have different thresholds to decide when to discontinue for toxicity (assuming that toxicity occurs at random). Another likely explanation is that these differences are more related to the drug used by each rheumatologist than the rheumatology thresholds. Of interest, rates of continuation for inefficacy were not statistically significant, which suggests that interpretation of inefficacy or lack of efficacy is similar among rheumatologists.

Table 6.4 shows the mean times of discontinuation for the different rheumatologists.

C. GENDER

There were no statistically significant gender differences with respect to rates of discontinuations due to any cause, toxicity (Figures 6.22 to 6.25). Overall, HCQ had a trend to have higher rates of continuation than CQ in males especially after 20 months (Figure 6.22). Rates of continuation due to inefficacy between males and females were different between CQ and HCQ (Figures 6.26 and 6.27). HCQ had higher rates of discontinuation in females and this was statistically significant (Figure 6.27).

D. DISEASE DURATION

There were 532 cases (57%) with a disease duration of less than 2 years while 340 cases (36%) had a disease duration of more than 2 years. In 68 cases (7%) it was not possible to establish the disease duration from the medical record and they were considered as a missing values. There were no statistically significant differences for the overall, toxicity and inefficacy rates of continuation between CQ and HCQ with respect to disease duration (Figures 6.28 to 6.33). However, in disease duration of more than 2 years HCQ had higher rates of discontinuation and this was a marginal statistically signficant difference ($p= 0.06$, Figure 6.33). CQ had a trend to higher rates of discontinuations in both groups (less than two years and more than two years of disease duration). However, HCQ had higher rates of discontinuation due to inefficacy only in disease duration of more than two years (Figure 6.33). Thus, a trend for CQ to be more toxic but also more effective than HCQ is seen.

E. RANK SELECTION

Overall, in 676 cases (72%) the AM were the first drug of choice as a second line drug. In 125 (13%) AM were the second drug of choice. Thus, in 85% of the cases AM were either the first or second drug chosen as a second line drug. A statistically significant difference with respect to rank selection was seen when AM where considered as a single group. Thus, first selection had higher continuation rates than other selection when all causes of discontinuation were plotted (Figure 6.34). The same findings were seen for toxicity discontinuations (Figure 6.35). No differences with respect to inefficacy were observed (Data not shown). This suggest that the earlier use of AM has a lower probability of discontinuation for any cause but inefficacy. On the other hand, when first selection was compared in each AM there was a statistically significant difference only in discontinuations due to inefficacy; with CQ having a higher continuation rates than HCQ (Fig.6.36). No differences were seen with respect to toxicity or all causes of discontinuation.

3. SIDE EFFECTS

Overall, there were 212 patients (22.5%) who had side effects while they were on AM therapy (Table 6.5). From these, only 145 (68%) discontinued the drug permanently (Table 6.6). It is important to mention that all but one of those patients who switched AM should be counted as permanently discontinued for the first AM). A significant difference with respect to side effects between CQ and HCQ was seen, with CQ having higher rates (Table 6.5)

The main side effects were ocular and gastrointestinal 7.4% and 7.1%, respectively. When particular side effects were analyzed, corneal deposits of the drug (keratopathy), blurred vision, rash, and myopathy were significantly

higher in patients who took CQ ($p<0.05$) (Table 6.5). In our study 41 patients (6.3%) had symptomatic corneal deposits. Thirty-eight (10.2%) from those who received CQ and had ophthalmologic evaluation (n=372) had symptomatic corneal deposits. Of interest, three patients were reported to have retinal changes that were suggestive of retinopathy (2 had RA and 1 had SLE). All of them received the AM at conventional doses (250 mg/day for CQ and 400 mg/day for HCQ). However, when they were sent to a retinologist with experience in retinopathy by AM, only one case was confirmed to have a probable incipient retinopathy. This patient had SLE and had received CQ for 59 months with a cumulative dose of 447.4 grams. The patient was followed and retinal changes disappeared. Nineteen months after CQ was discontinued she received HCQ, with no recurrence of the retinal changes at her most recent ophthalmologic evaluation.

In addition, myopathy was seen only in patients who received CQ and this was statistically significant.

4. SUMMARY

In summary, crude rates for antimalarial discontinuations showed that CQ is more toxic than HCQ (18% vs. 12% respectively; $p=0.01$). However, rates of discontinuations due to inefficacy were higher for HCQ, although the difference did not reach statistical significance (21% vs. 17%). After adjusting for time and for censoring data (Kaplan-Meier method) similar conclusions can be drawn. Firstly, there were no statistically significant differences between CQ and HCQ with respect to all causes of discontinuations in any of the potential confounders, except for rheumatologist and disease type. Thus, it seems that there are no differences between CQ and HCQ in the long-term when all causes of discontinuations are evaluated. Second, when causes of discontinuations were split in two groups: a) discontinuations due to toxicity

and b) discontinuations due to inefficacy, important differences were seen. Overall, CQ had a trend to lower rates of continuation than HCQ in all the variables evaluated (disease type, specific disease group, disease duration, gender, and type of antimalarial). However, the only variable in which a statistically significant difference was observed was PA. Of interest, all variables showed a trend for higher rates of continuation for HCQ. Finally, discontinuations due to inefficacy were statistically significant for type of antimalarial, disease type, disease duration, and gender. In all CQ had higher rates of continuation than HCQ. Thus, adjustment for these variables must be done when discontinuations due to inefficacy are being made.

Table 6.1. Causes of discontinuation in general for AM by drug.

	AM n(%)	CQ n(%)	HCQ n(%)
Total receiving therapy	**940 (100)**	**541 (57)**	**399 (42)**
Still on	468 (50)	251 (46)	271 (54)
Toxicity	145 (15)	97 (18)	48 (12)
Inefficacy	175 (19)	93 (17)	82 (21)
Other causes	129 (14)	87 (9)	42 (4)
no longer needed	27 (3)	17 (3)	10 (3)
by patient	63 (7)	44 (8)	19 (5)
pregnancy	14 (2)	12 (2)	2 (.5)
concomitant disease	19 (2)	12 (2)	7 (2)
other	6 (.6)	2 (.4)	4 (1)
uncertain	23 (2)	13 (2)	10 (3)

Table 6.2. Mean times to discontinuation between CQ and HCQ.

	OVERALL months (95% CI)		TOXICITY months (95% CI)		INEFFICACY months (95% CI)	
AM	47	(42-51)	89	(82-95)	83	(78-89)
CQ	47	(42-52)	86	(79-93)	87	(80-93)
HCQ	38	(34-43)	72	(68-75)	58	(53-63) (*)

(*) $p < 0.01$ CQ vs HCQ

Table 6.3 Mean times to discontinuation among all disease groups.

	OVERALL months (95% CI)		**TOXICITY months (95% CI)**		**INEFFICACY months (95% CI)**	
SLE	62	(52-72) (*)	97	(88-106)	105	(96-113) (*)
RA	39	(35-44)	75	(69-82)	64	(58-70)
PA	47	(36-57)	80	(65-94)	80	(68-91)
OTHER	38	(31-45)	57	(51-63)	53	(46-60)

(*) $p < 0.001$ comparing all disease groups

Table 6.4 Mean times of discontinuation among rheumatologists.

	OVERALL		TOXICITY		INEFFICACY	
	months	95% CI	months	95% CI	months	95% CI
Rh1	51	(45-58) (*)	82	(75-88) (**)	77	(70-83)
Rh2	42	(31-53)	82	(65-99)	82	(68-96)
Rh3	58	(43-73)	96	(85-108)	94	(80-108)
Rh4	40	(28-52)	76	(66-87)	65	(46-83)
Rh5	31	(26-36)	54	(50-58)	43	(38-49)
Rh6	39	(34-45)	75	(68-81)	67	(60-74)
Rh7	40	(18-62)	59	(31-88)	74	(62-87)

(*) $p < 0.03$ comparing all rheumatologists
(**) $p < 0.05$ comparing all rheumatologists

Table 6.5. Side effects between AM.

Side effect	AM n(%)	CQ n(%)	HCQ n(%)	p value
Mucocutaneous	**33 (2.6)**	**25 (4.7)**	**8 (2)**	**NS**
Rash	31 (2.4)	23 (4.3)	8 (2)	<0.05
Hair bleaching	2 (0.2)	2 (0.4)	0 (0)	NS
Ocular	**70 (7.4)**	**63 (11.6)**	**9 (2.2)**	**<0.0001**
Corneal deposits	41 (4.4)	38 (7)	3 (0.8)	<0.00001
Blurred vision	26 (2.8)	21 (3.9)	5 (1.3)	<0.01
Retinal changes (*)	3 (0.3)	2 (0.3)	1 (0.2)	NS
Gastrointestinal	**67 (7.1)**	**34 (6.2)**	**33 (8.3)**	**NS**
Nausea/vomit	46 (4.9)	26 (4.8)	20 (5)	NS
Diarrhoea	14 (1.5)	5 (0.9)	9 (2.3)	NS
Abdominal pain	7 (0.7)	3 (0.6)	4 (1)	NS
Neuro-muscular	**19 (2)**	**17 (3.1)**	**2 (0.5)**	**NS**
Headache	9 (1)	7 (1.3)	2 (0.5)	NS
Nightmares	4 (0.4)	4 (0.7)	0 (0.0)	NS
Myopathy	6 (0.6)	6 (1.1)	0 (0)	0<0.03
Unknown	**23 (2.4)**	**16 (2.9)**	**7 (1.7)**	**NS**
TOTAL	**212 (22.5)**	**153 (28.2)**	**59 (14.7)**	**<0.00001**

NS= not significant

(*) Only one patient was confirmed to have a true retinopathy (see text).

Table 6.6. Side effects outcome.

OUTCOME	AM n(%)	CQ n(%)	HCQ n(%)	p value
No DC	43 (20)	41(27)	2 (3)	<0.0001
DC Permanently	119 (56)	72 (47)	47 (78)	NS
DC Temporarily	11 (5)	5 (3)	6 (10)	NS
Decrease dose	12 (6)	9 (6)	3 (5)	NS
Switched AM	27 (13)	26 (17)	1 (2)	<0.0001
Total	**212(100)**	**153 (72)**	**59 (28)**	

DC= discontinuation NS= not significant

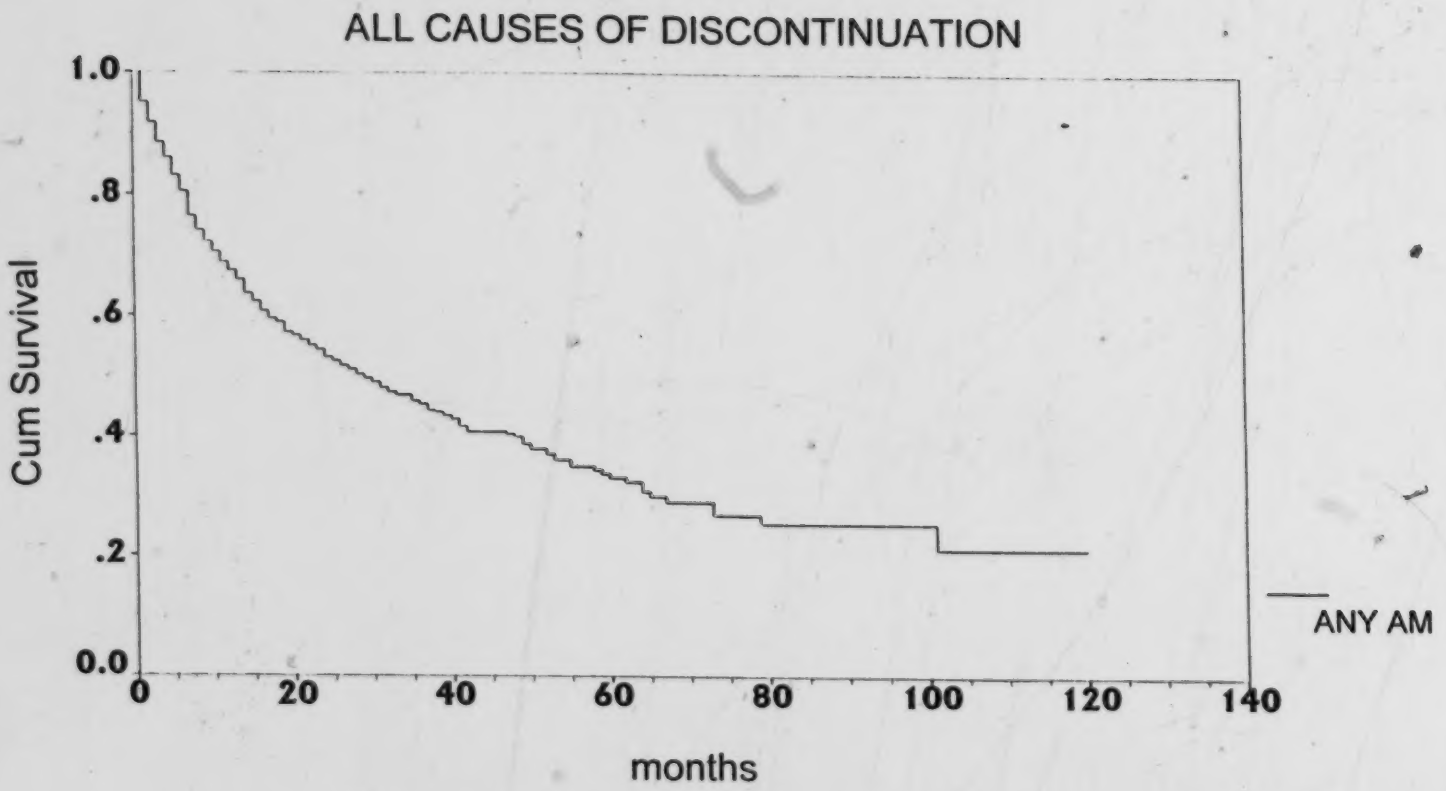

Figure 6.1 Kaplan-Meier for all causes of discontinuations for any AM.

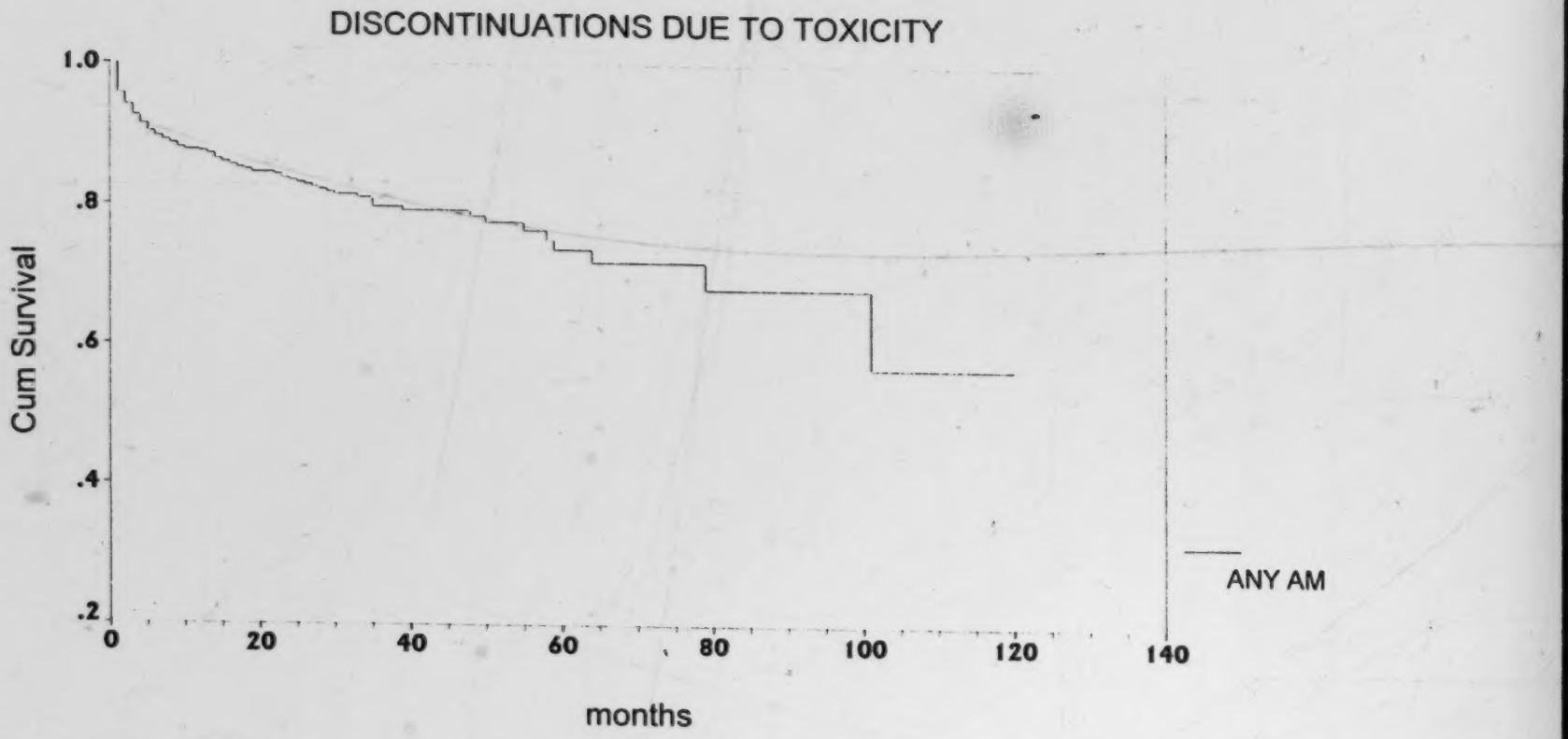

Figure 6.2 Kaplan-Meier for discontinuations due to toxicity for any AM.

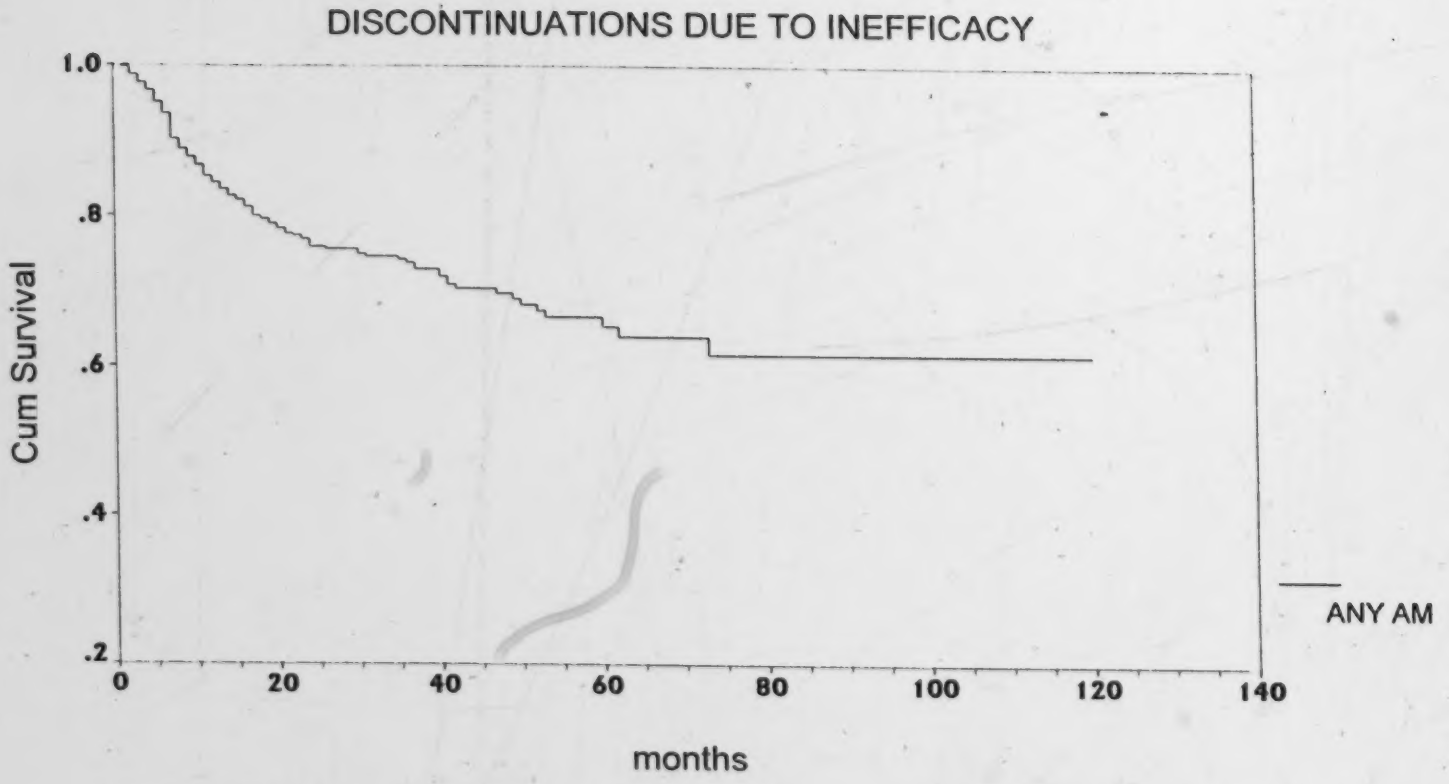

Figure 6.3 Kaplan-Meier for discontinuations due inefficacy for any AM.

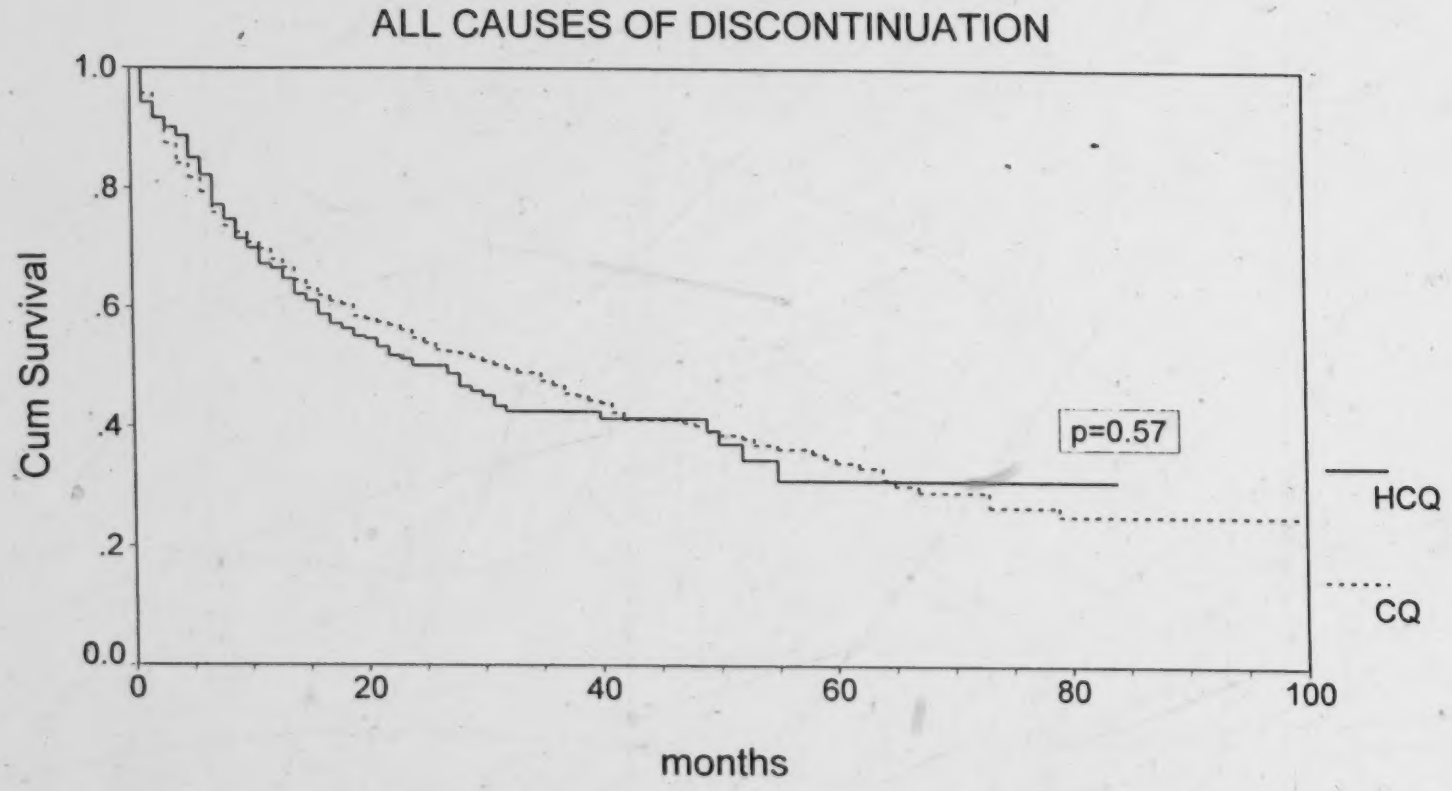

Figure 6.4 Kaplan-Meier curves for all causes of discontinuations

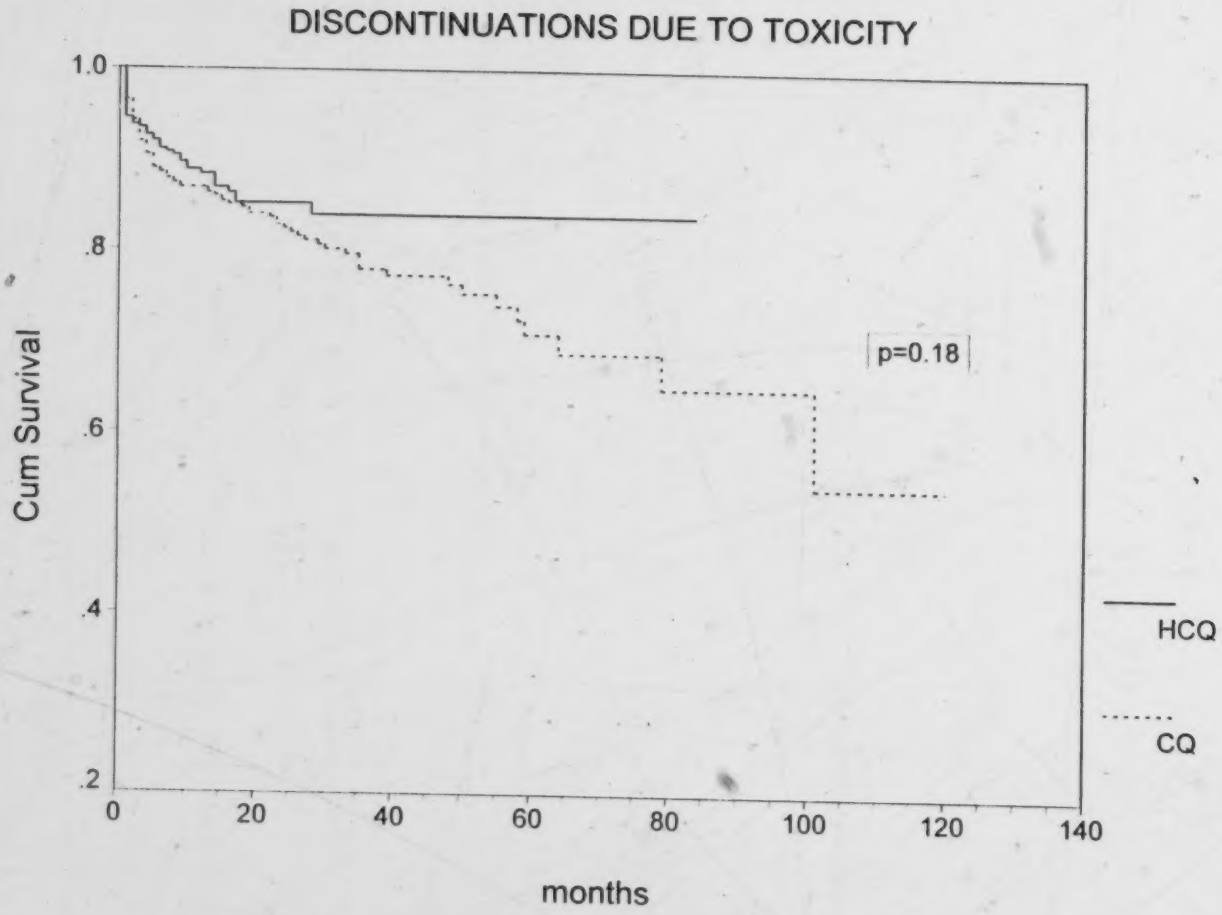

Figure 6.5 Kaplan-Meier curves for discontinuations due to toxicity

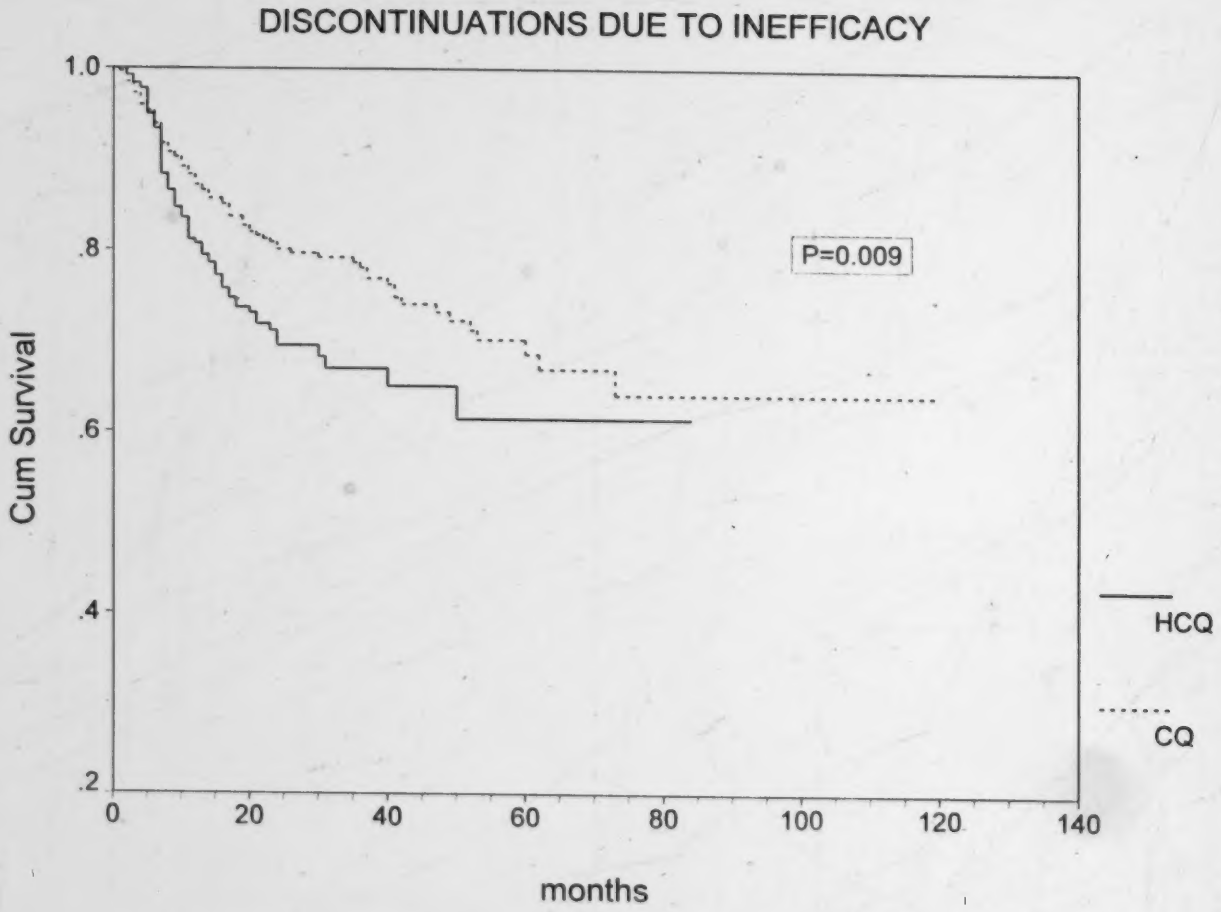

Figure 6.6 Kaplan-Meier curves for discontinuations due to inefficacy

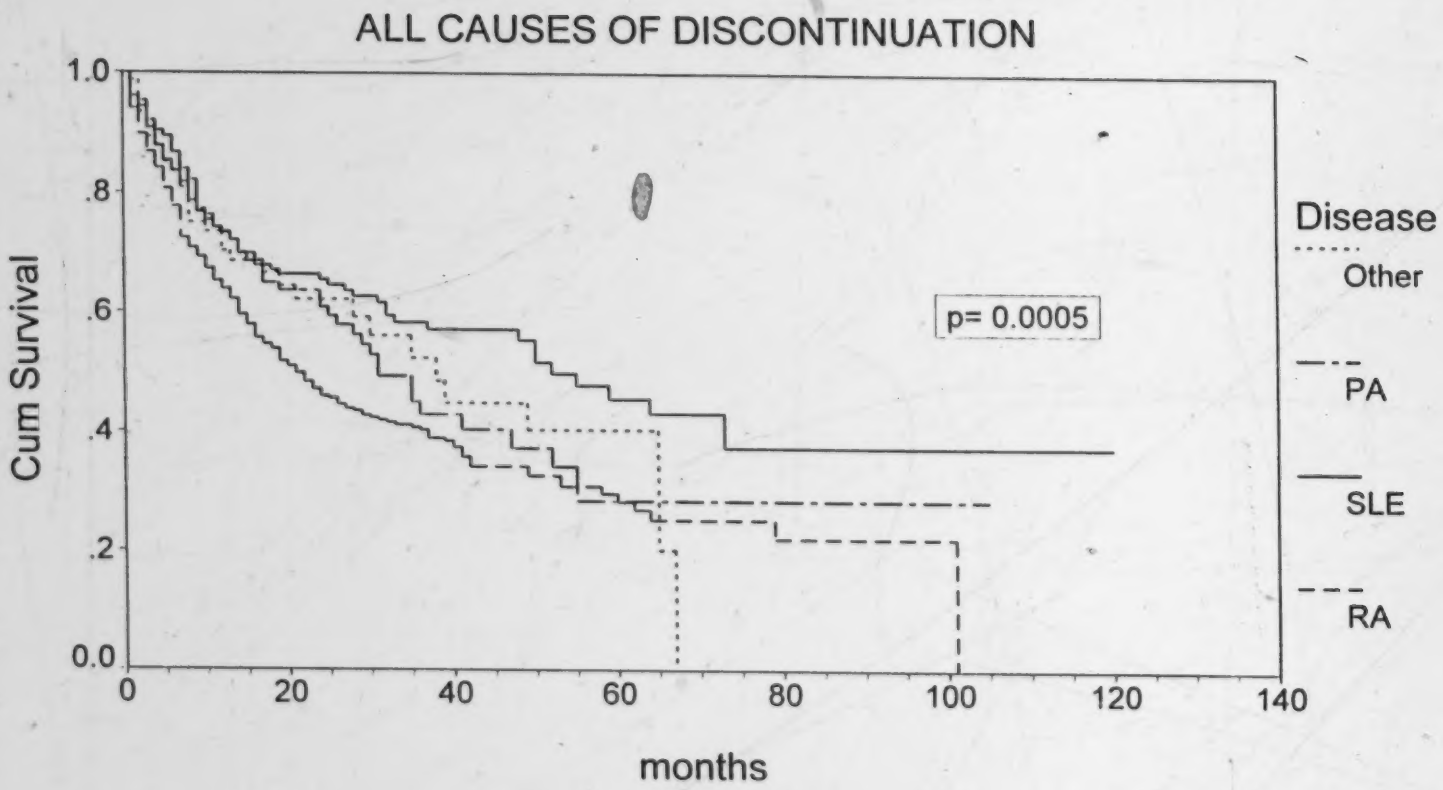

Figure 6.7 Kaplan-Meier curves for all discontinuations by disease group

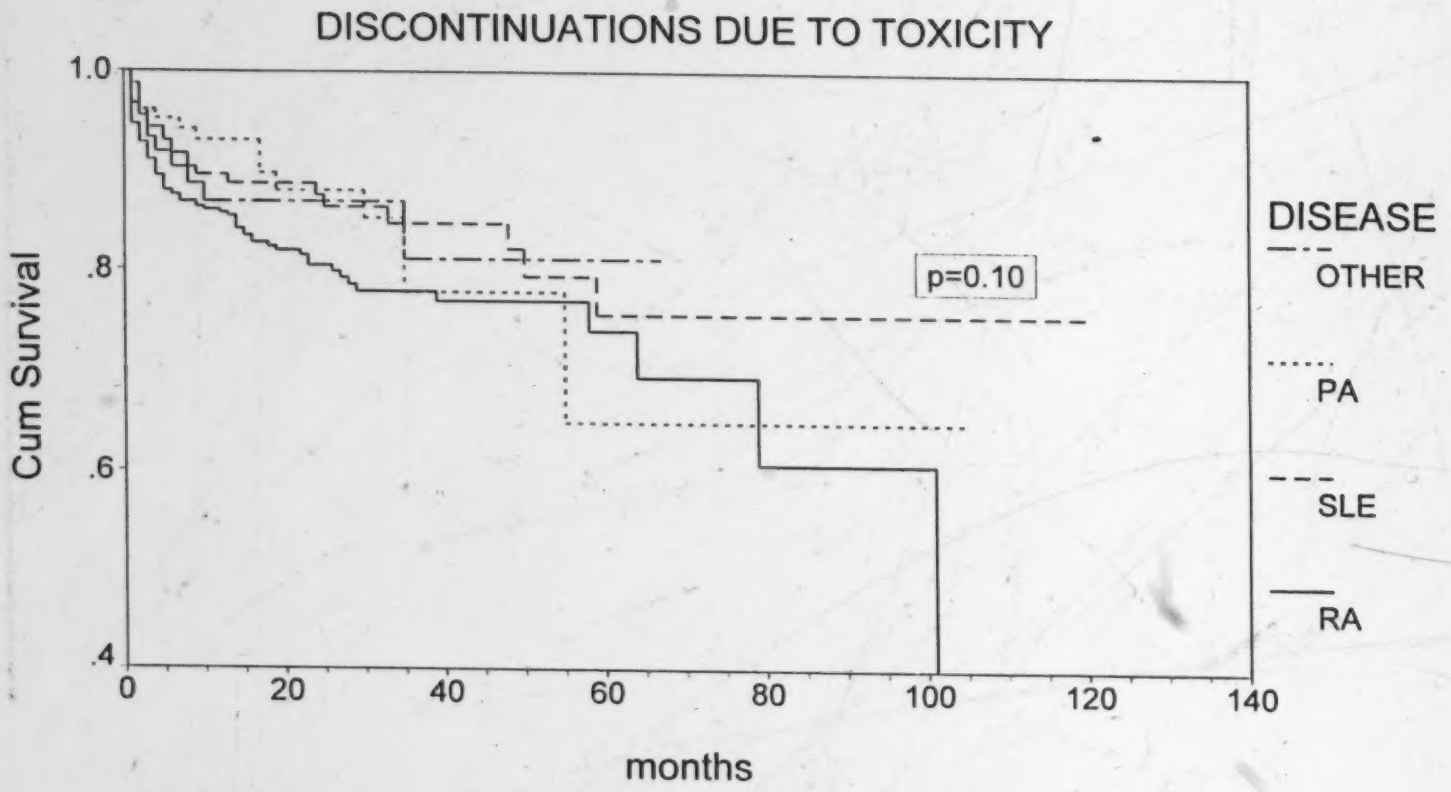

Figure 6.8 Kaplan-Meier for toxicity among disease groups

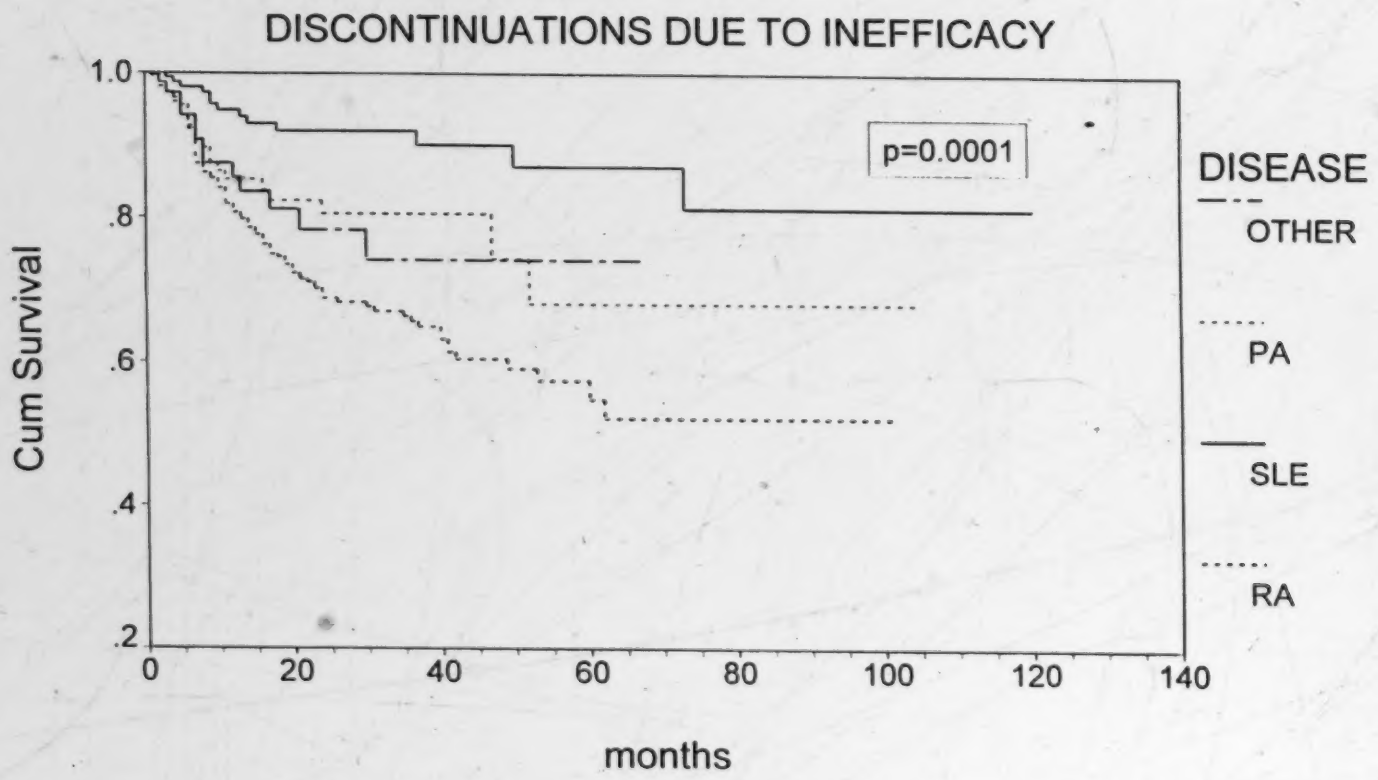

Figure 6.9 Kaplan-Meier for inefficacy among disease groups

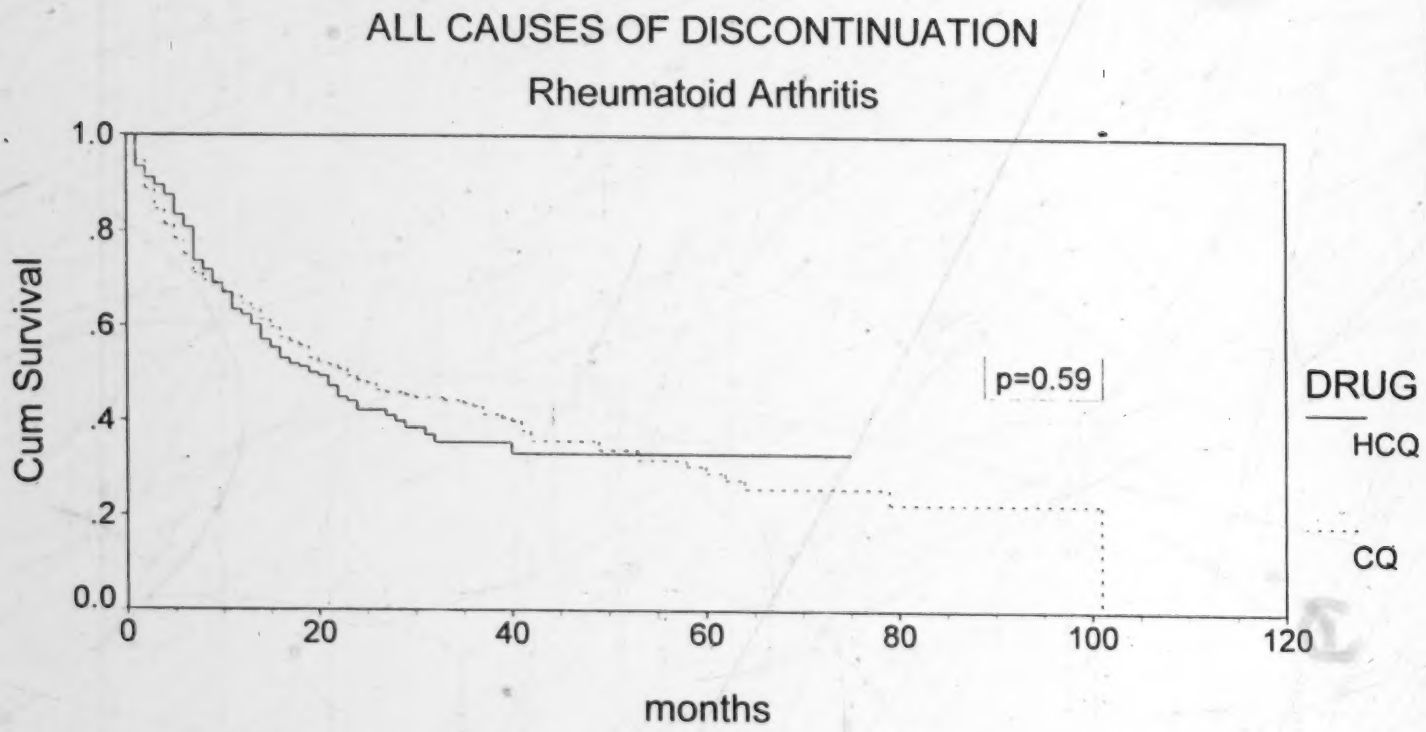

Figure 6.10 Kaplan-Meier for all causes of discontinuation for RA by type of antimalarial

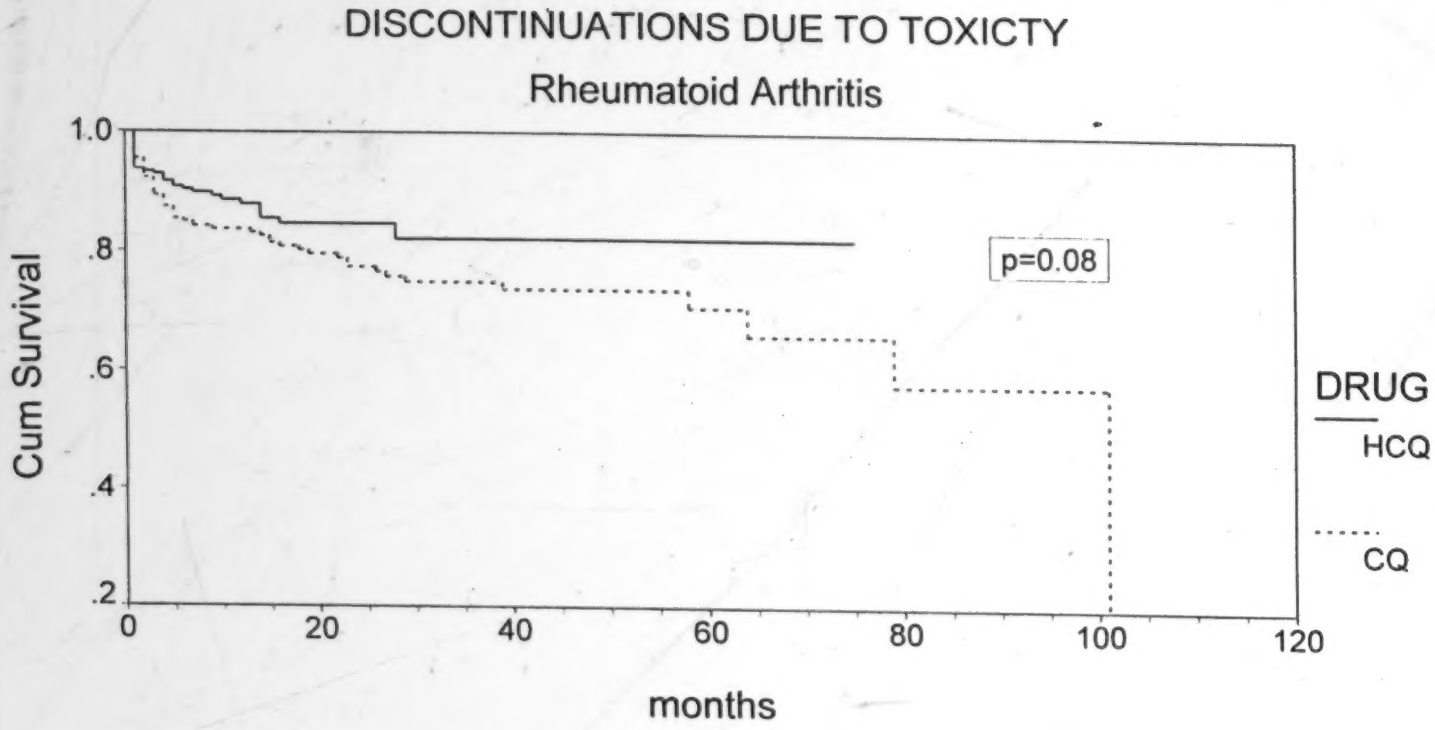

FIgure 6.11 Kaplan-Meier curves for toxicity in rheumatoid arthritis and by type of antimalarial.

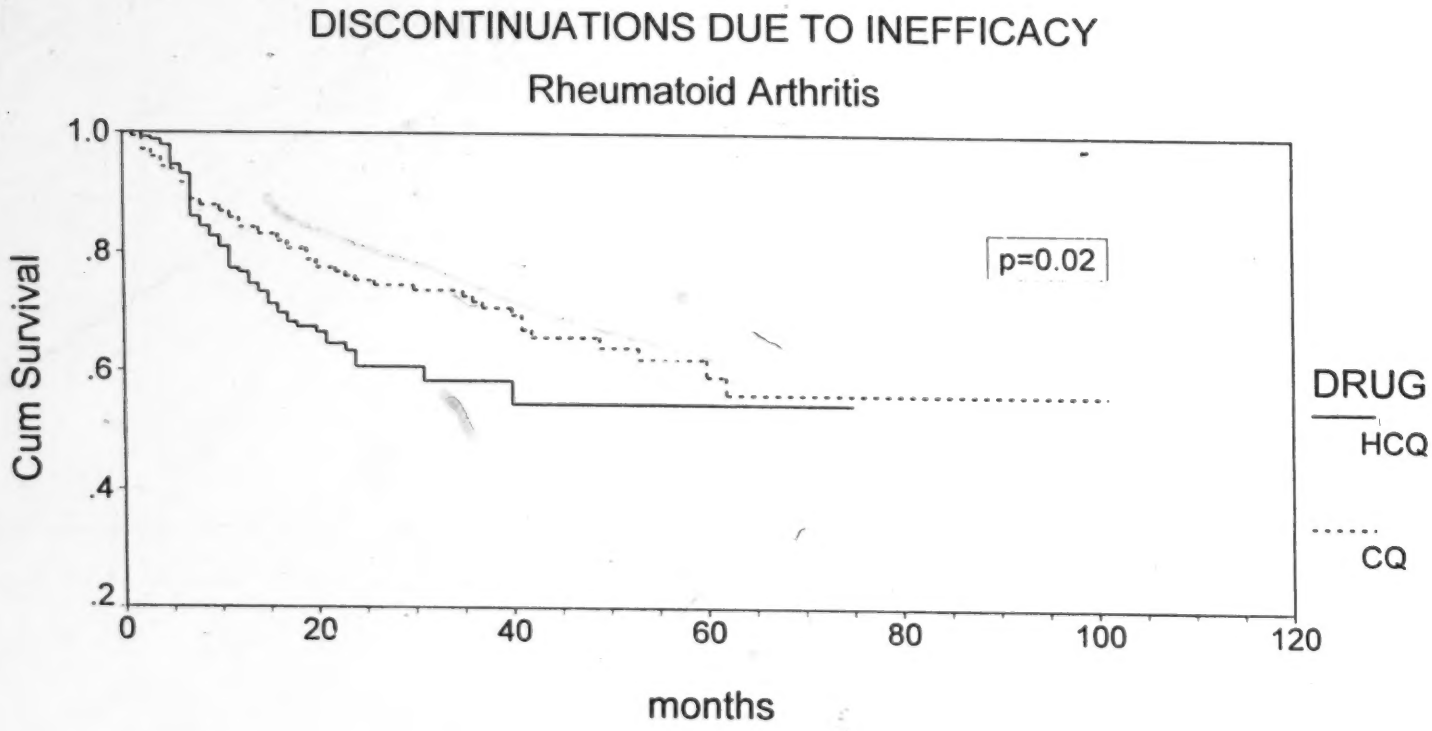

FIgure 6.12 Kaplan-Meier curves for inefficacy in rheumatoid arthritis and by type of antimalarial.

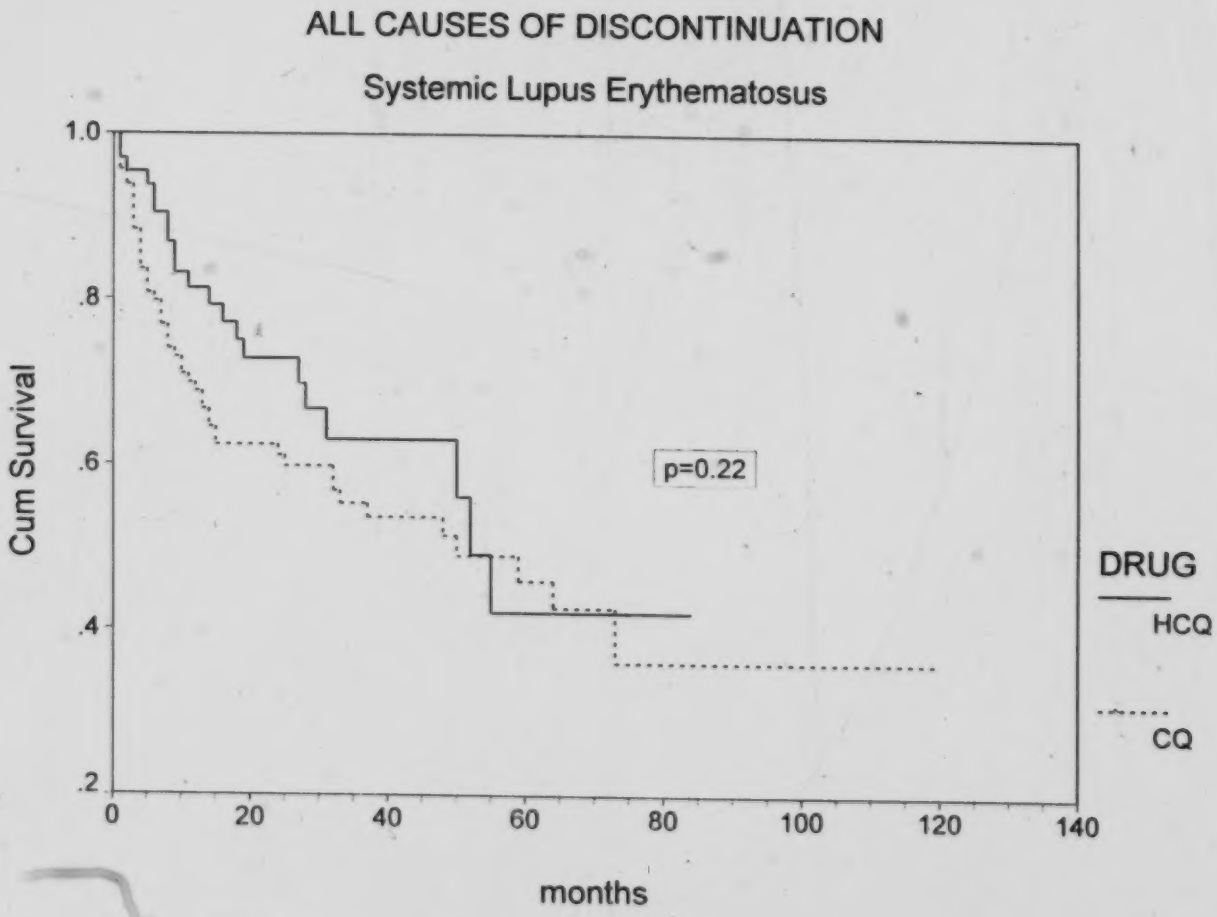

Figure 6.13. Kaplan-Meier curves for all discontinuations in SLE by drug

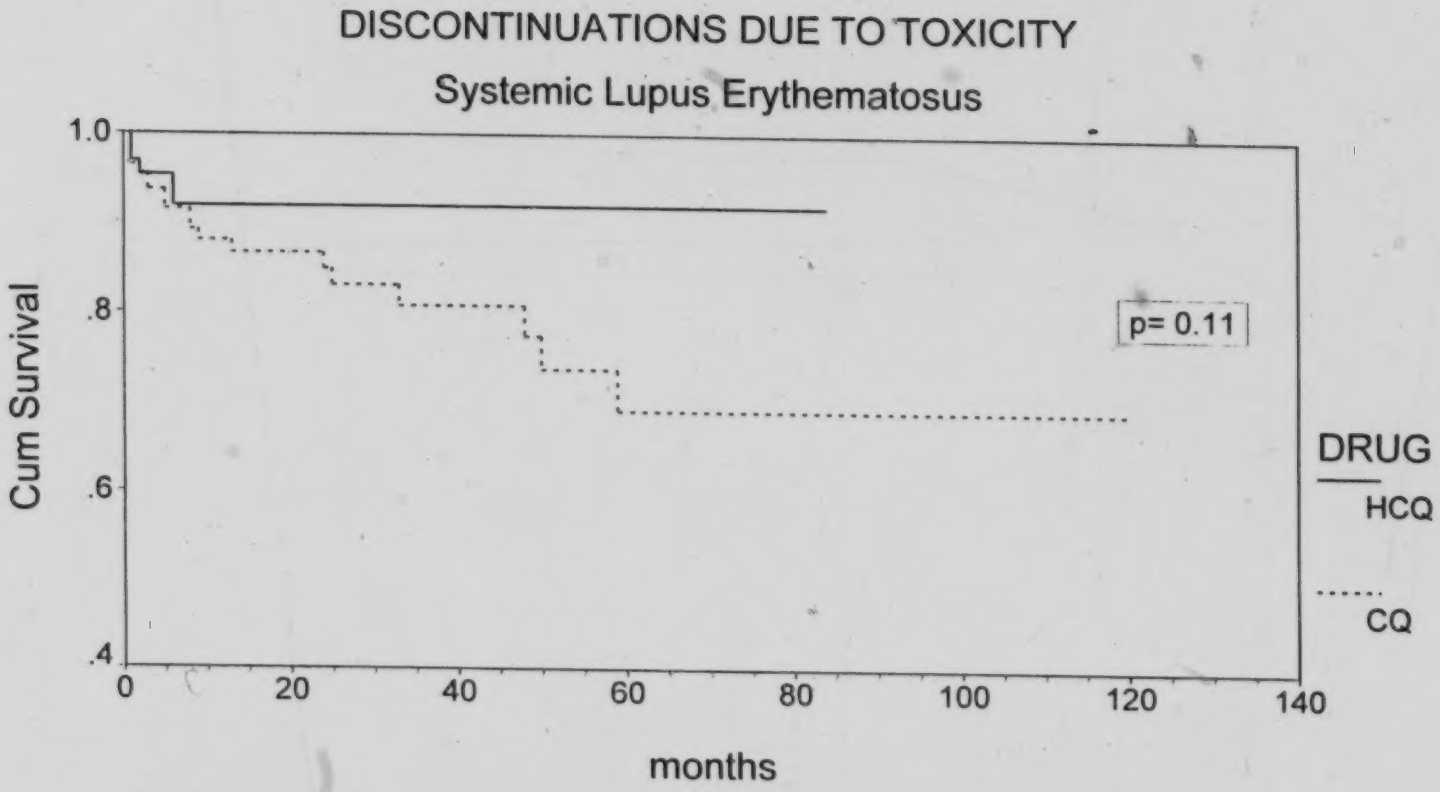

Figure 6.14 Kaplan-Meier curves for toxicity in SLE by drug.

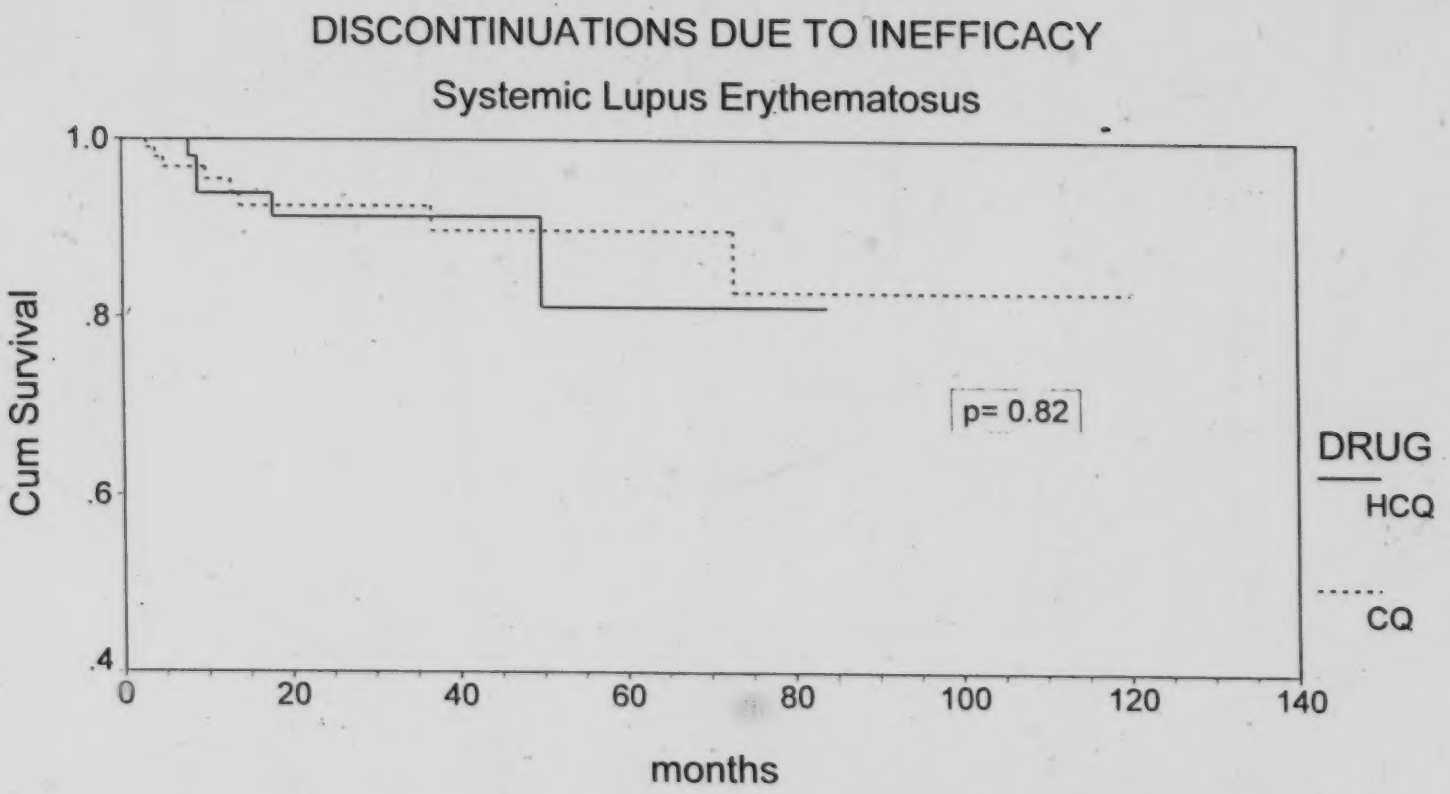

Figure 6.15 Kaplan-Meier curves for inefficacy in SLE by drug.

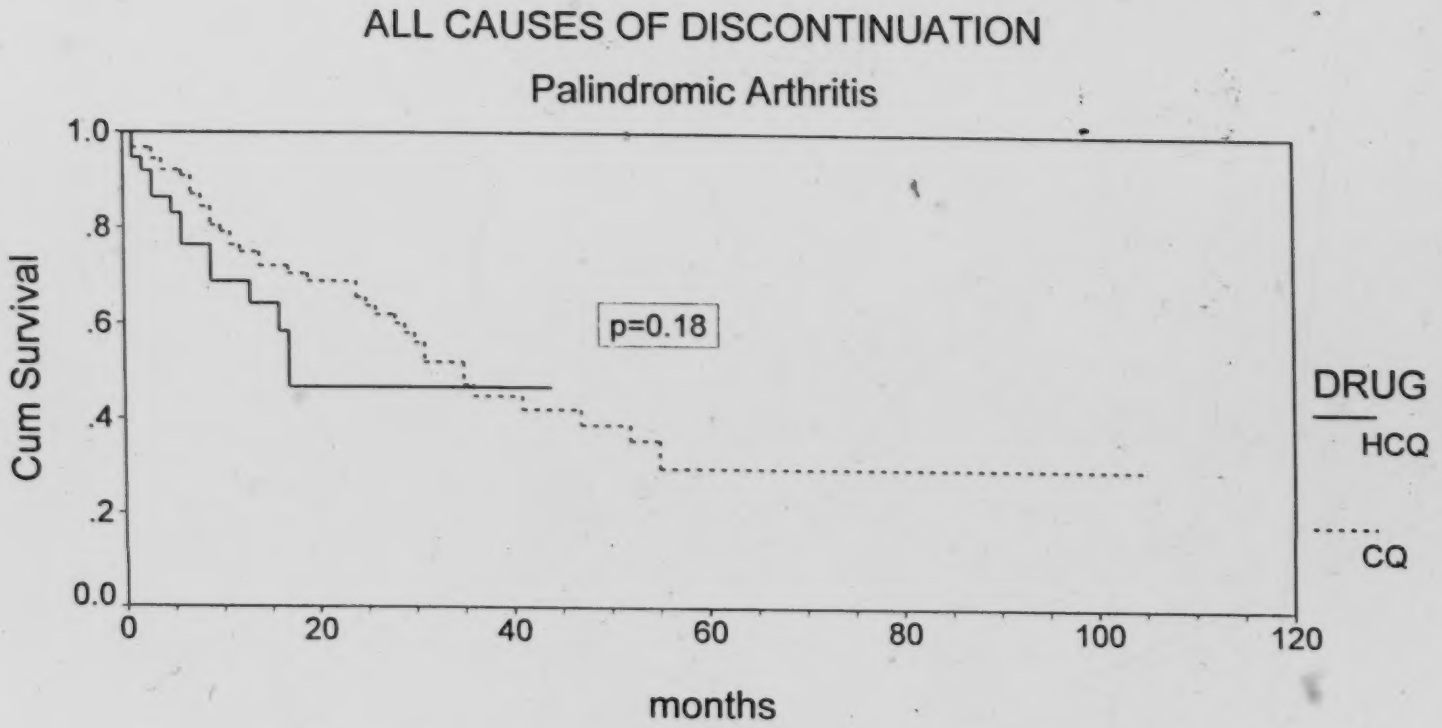

Figure 6.16. Kaplan-Meier curves for all causes of discontinuation in palindromic arthritis by drug.

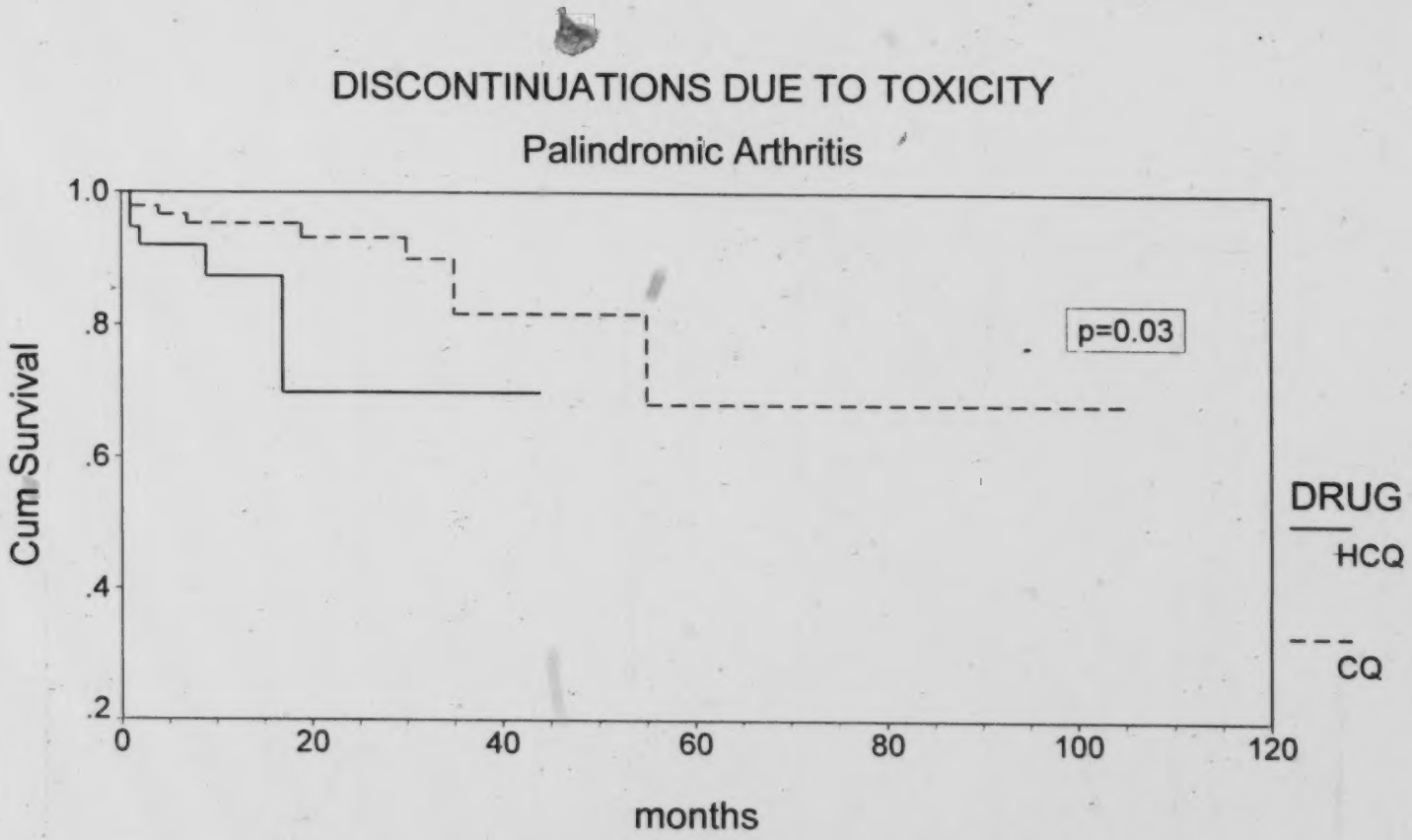

Figure 6.17 Kaplan-Meier curves for toxicity in PA by drug

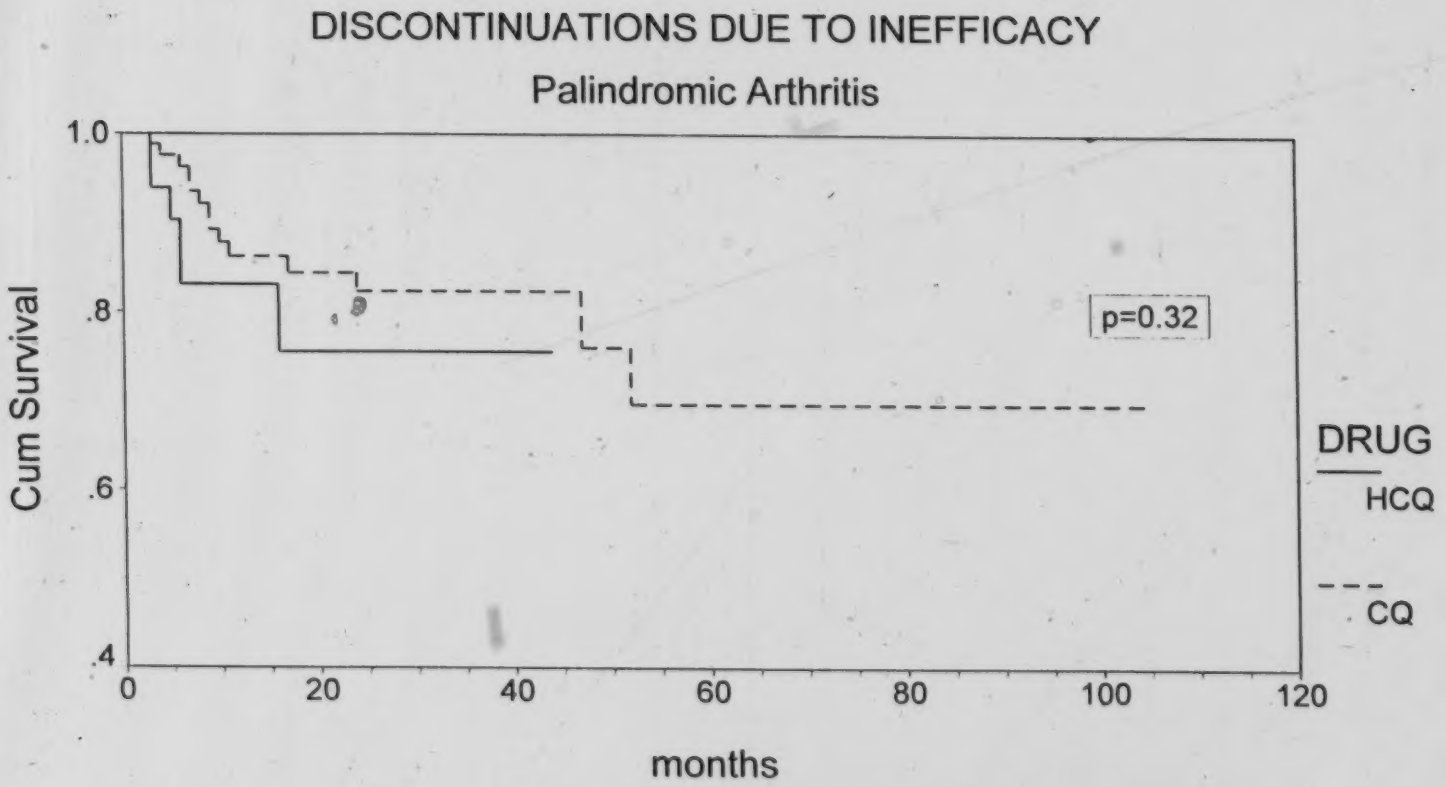

Figure 6.18 Kaplan-Meier curves for inefficacy in PA by drug

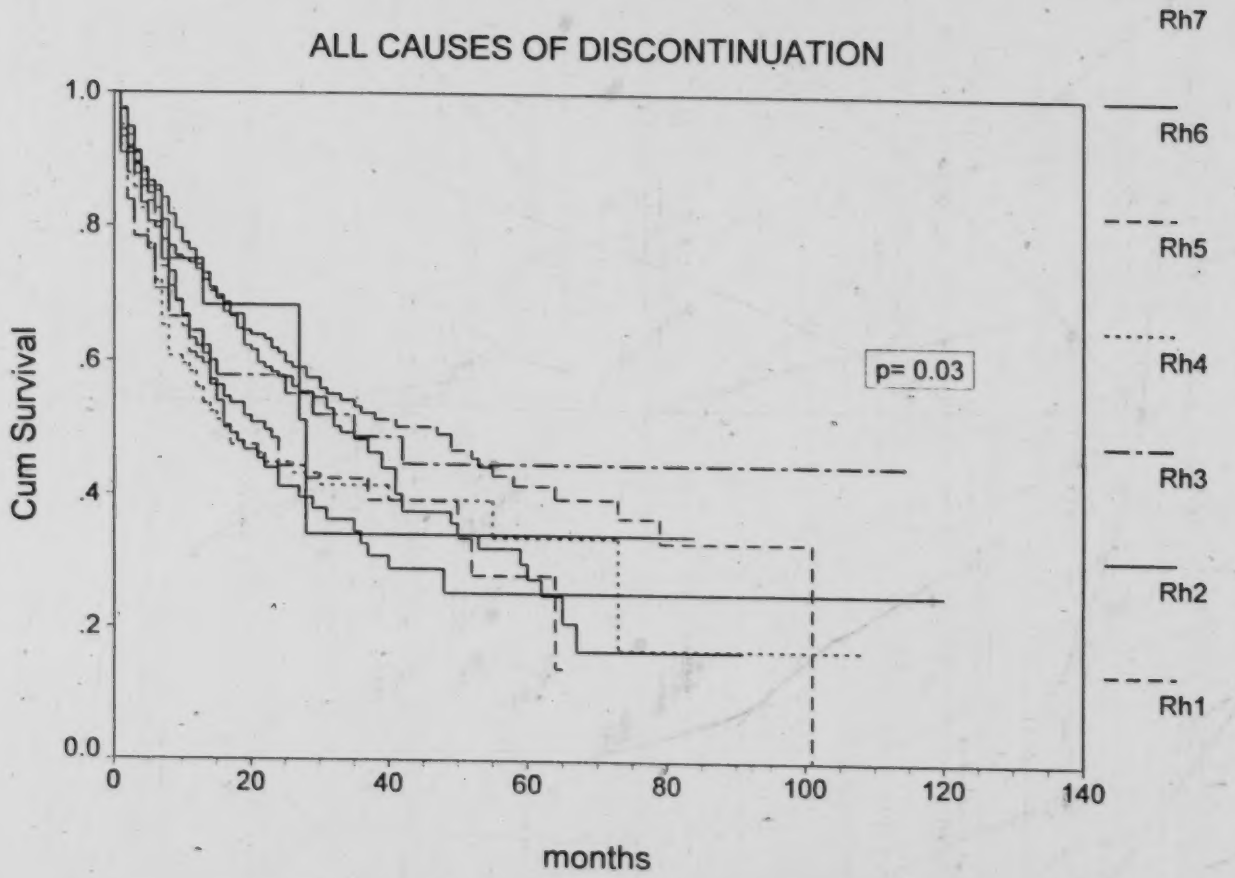

Figure 6.19 Kaplan-Meier curves for all causes of discontinuation among rheumatologists

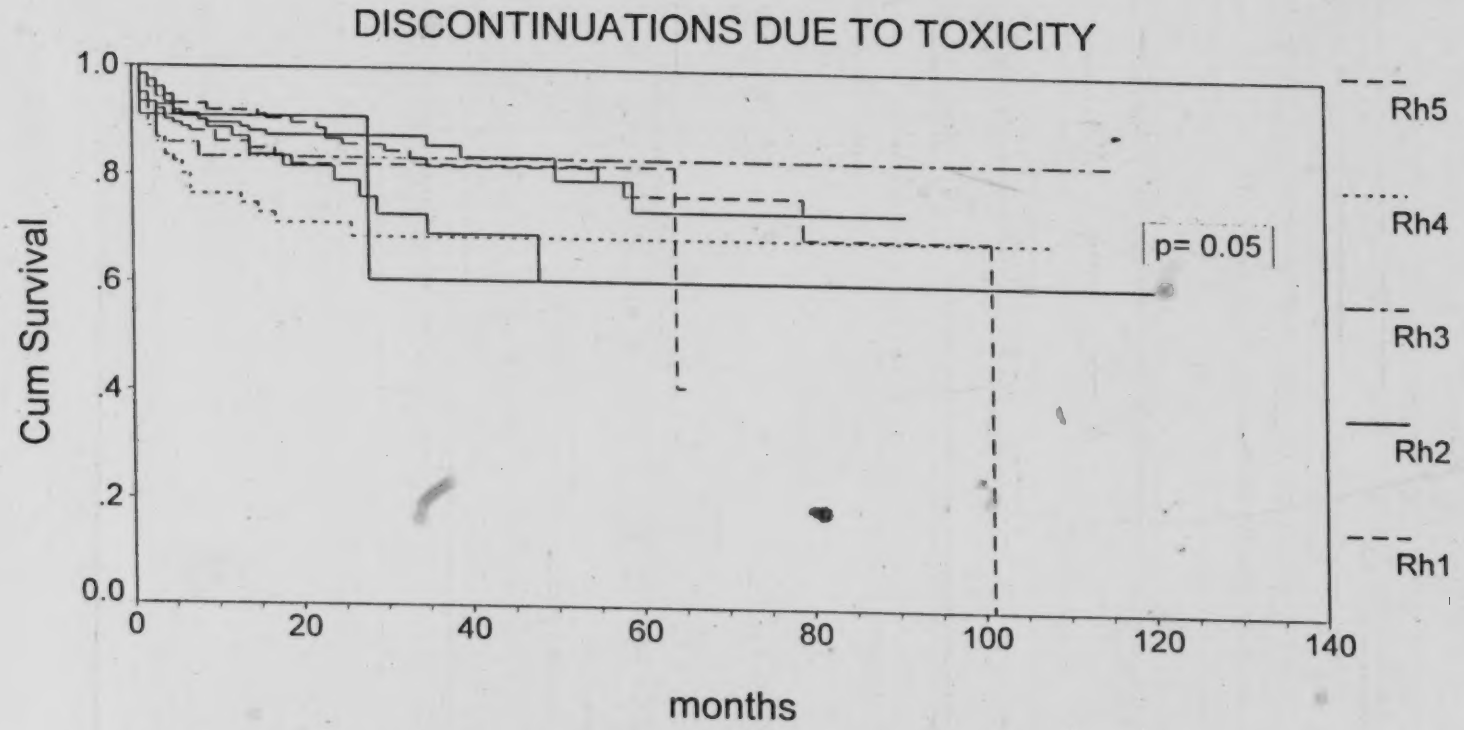

Figure 6.20 Kaplan-Meier curves for toxicity discontinuations among rheumatologists

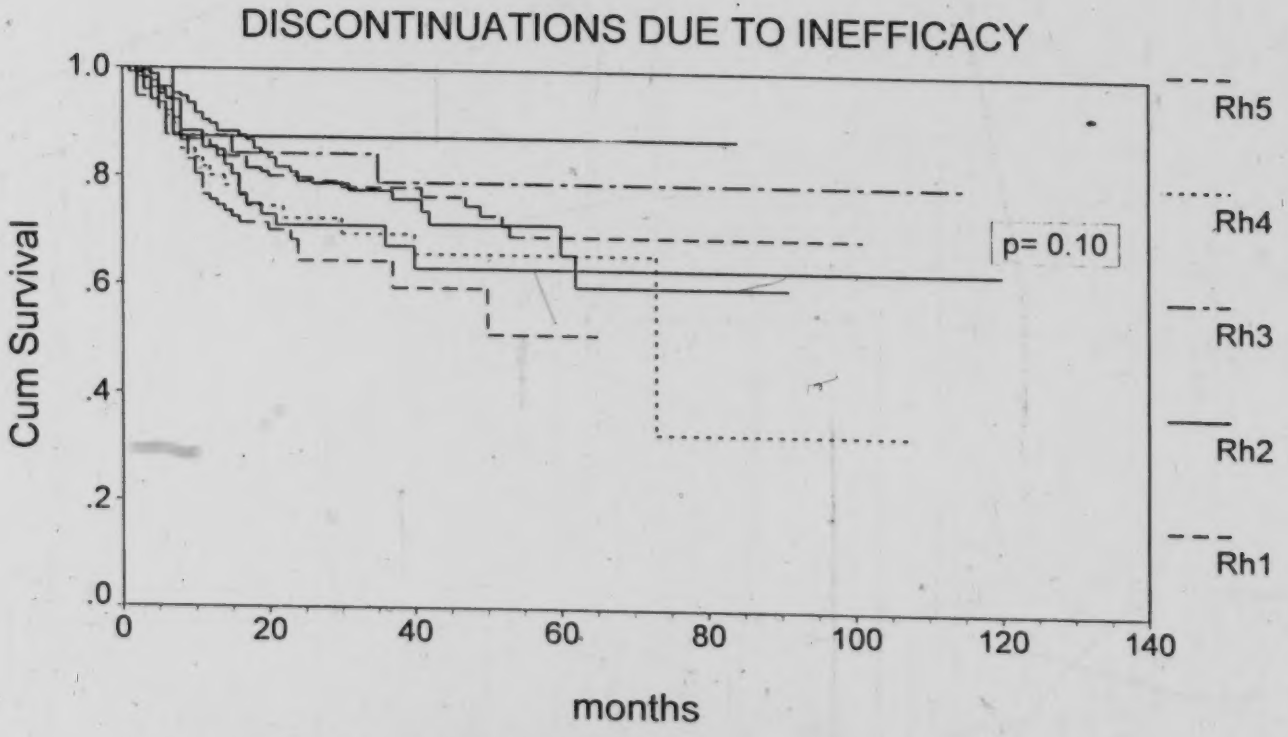

Figure 6.21 Kaplan-Meier curves for inefficacy discontinuations among rheumatologists

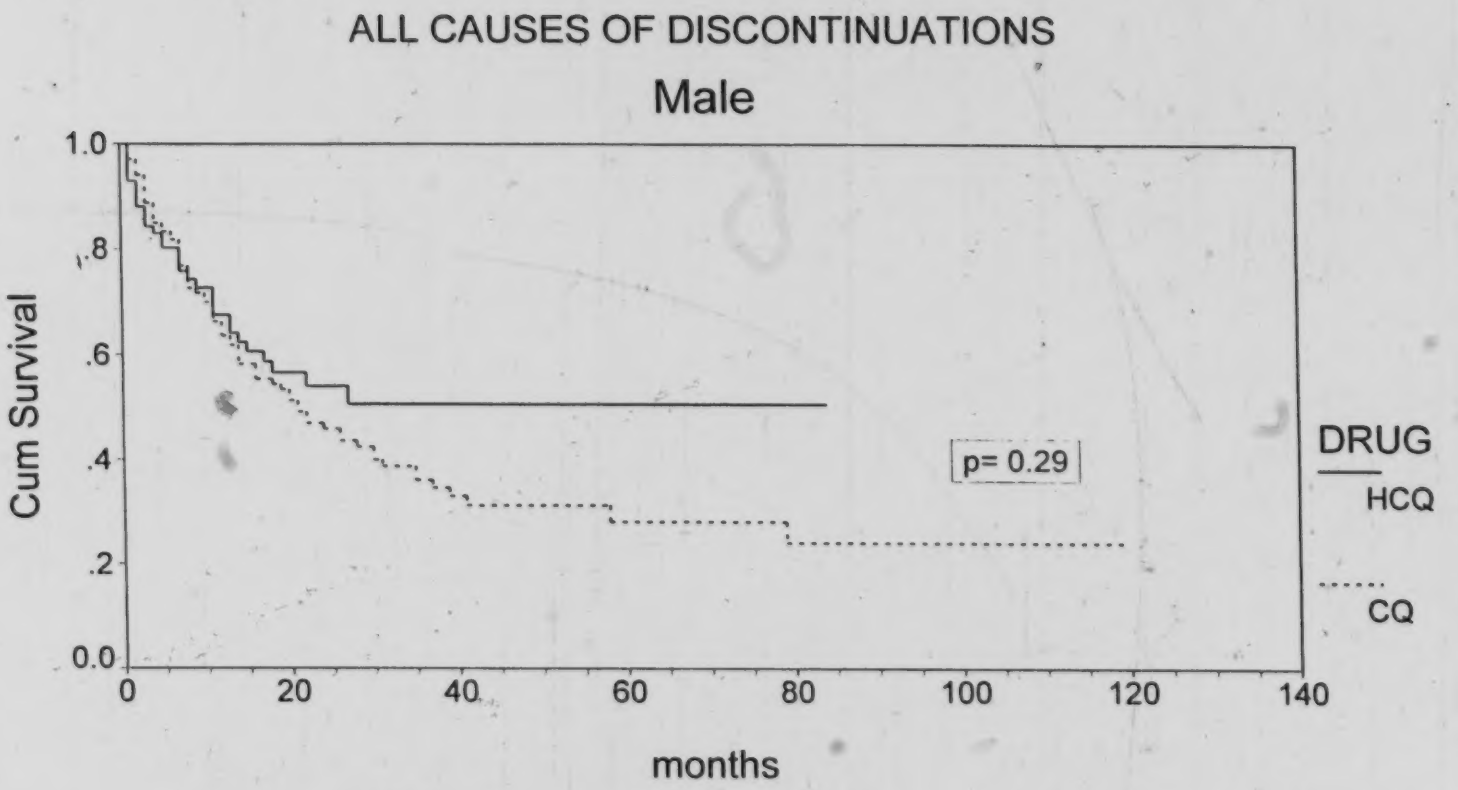

Figure 6.22. Kaplan-Meier curves for males by type of antimalarial

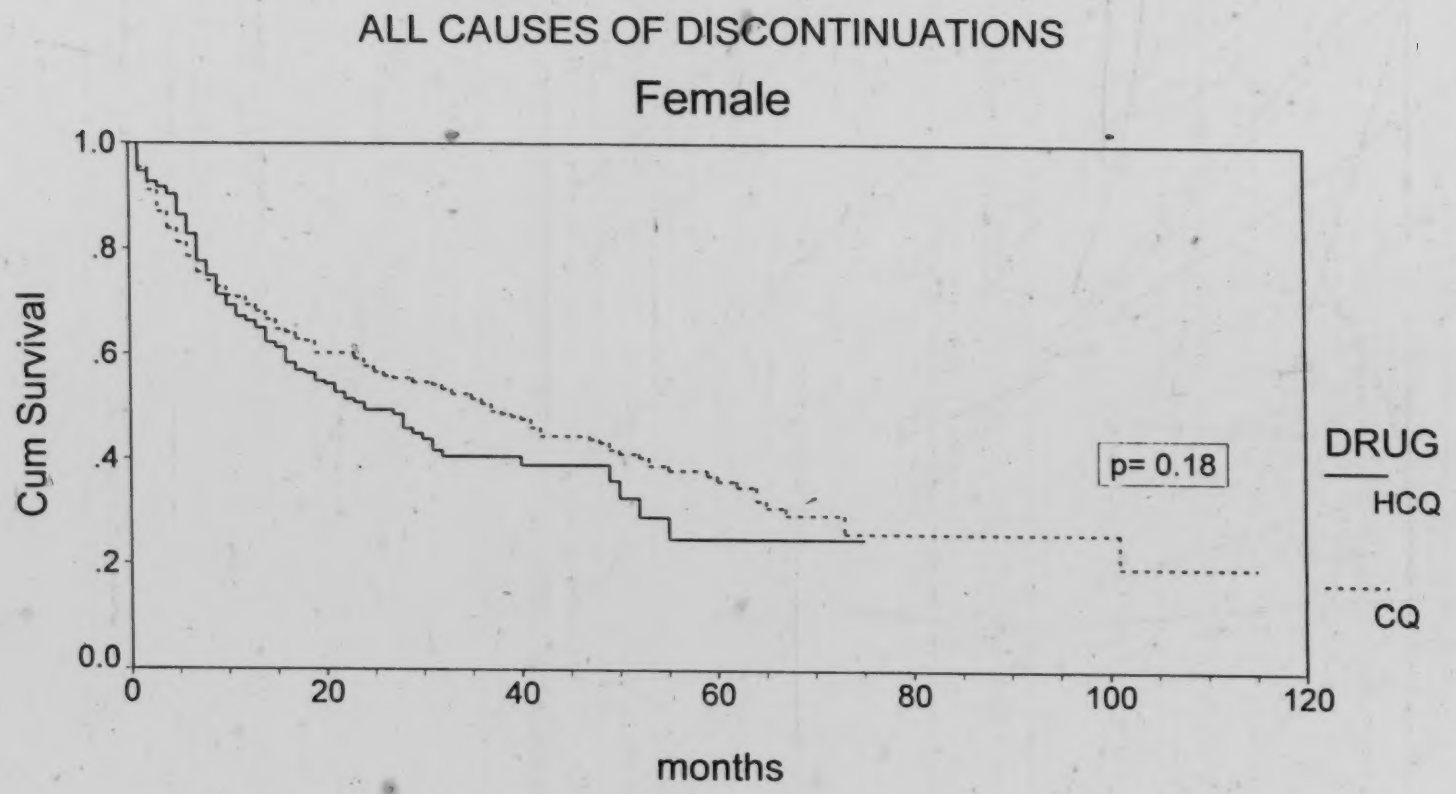

Figure 6.23 Kaplan-Meier curves for females by type of antimalarial

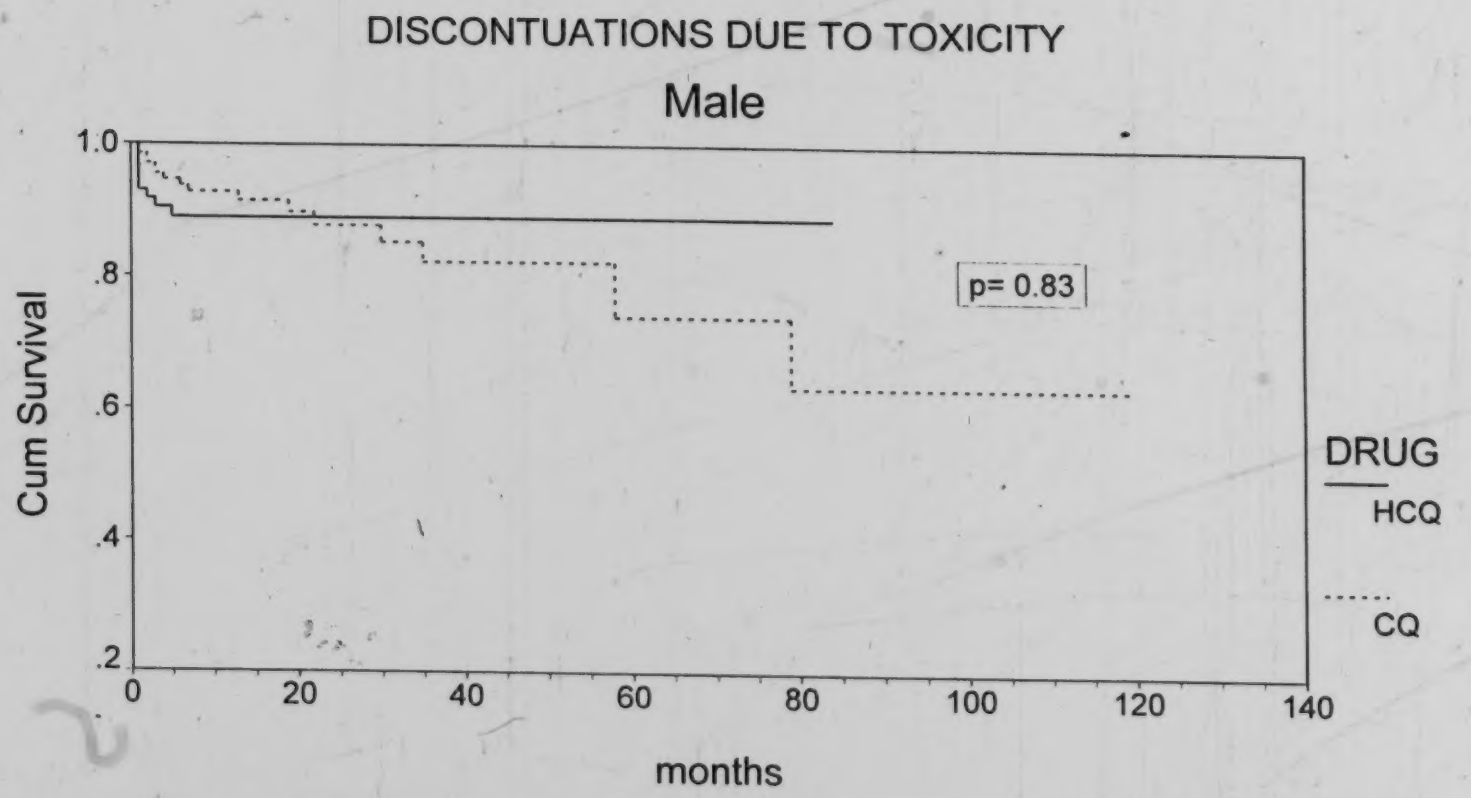

Figure 6.24 Kaplan-Meier curves for males by type of antimalarial

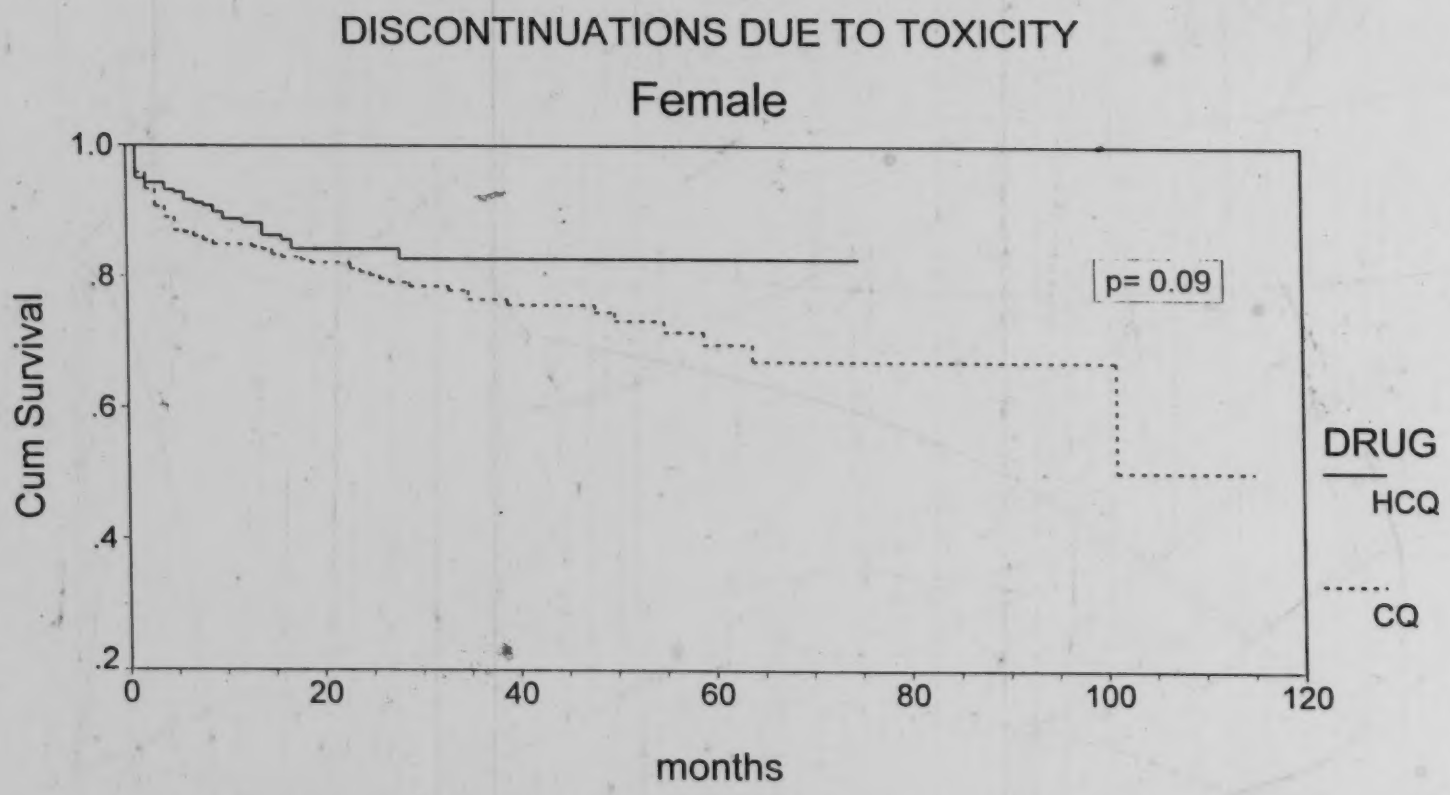

Figure 6.25 Kaplan-Meier curves for females by type of antimalarial

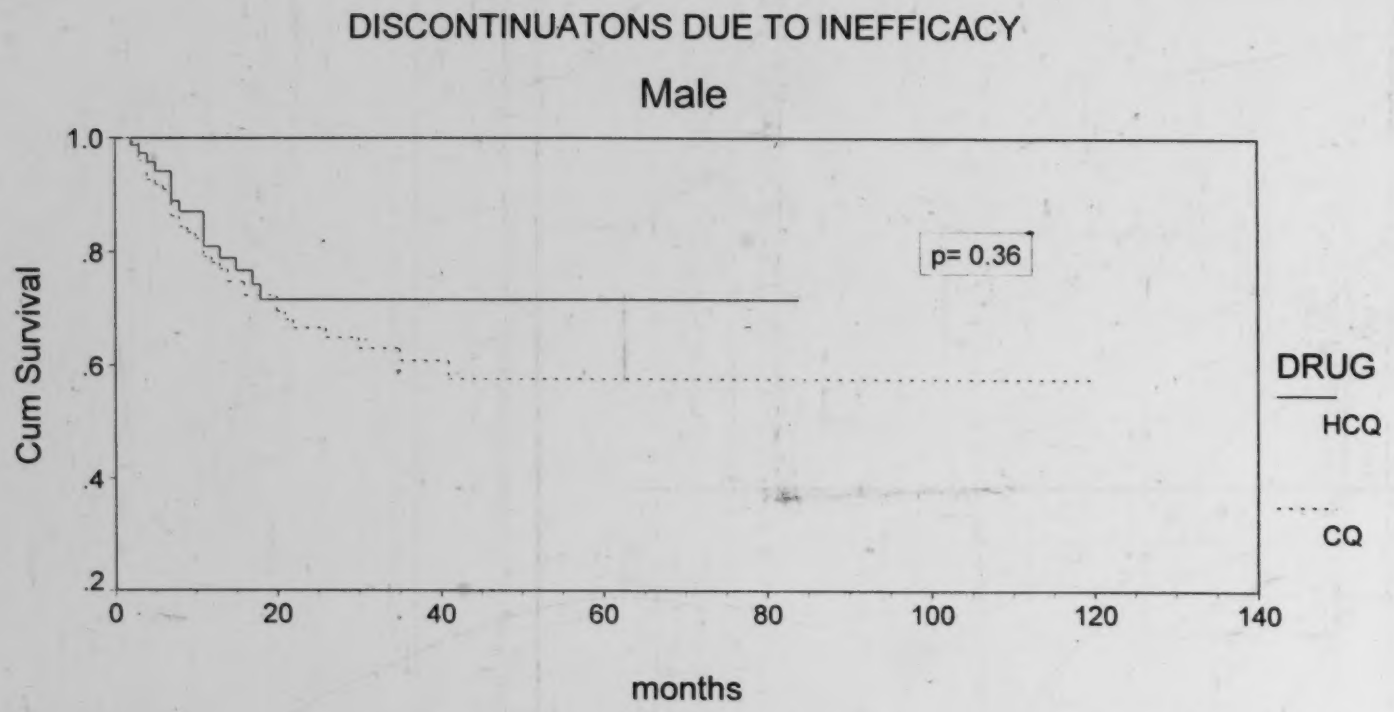

Figure 6.26 Kaplan-Meier curves for discontinuations due to inefficacy in males by drug.

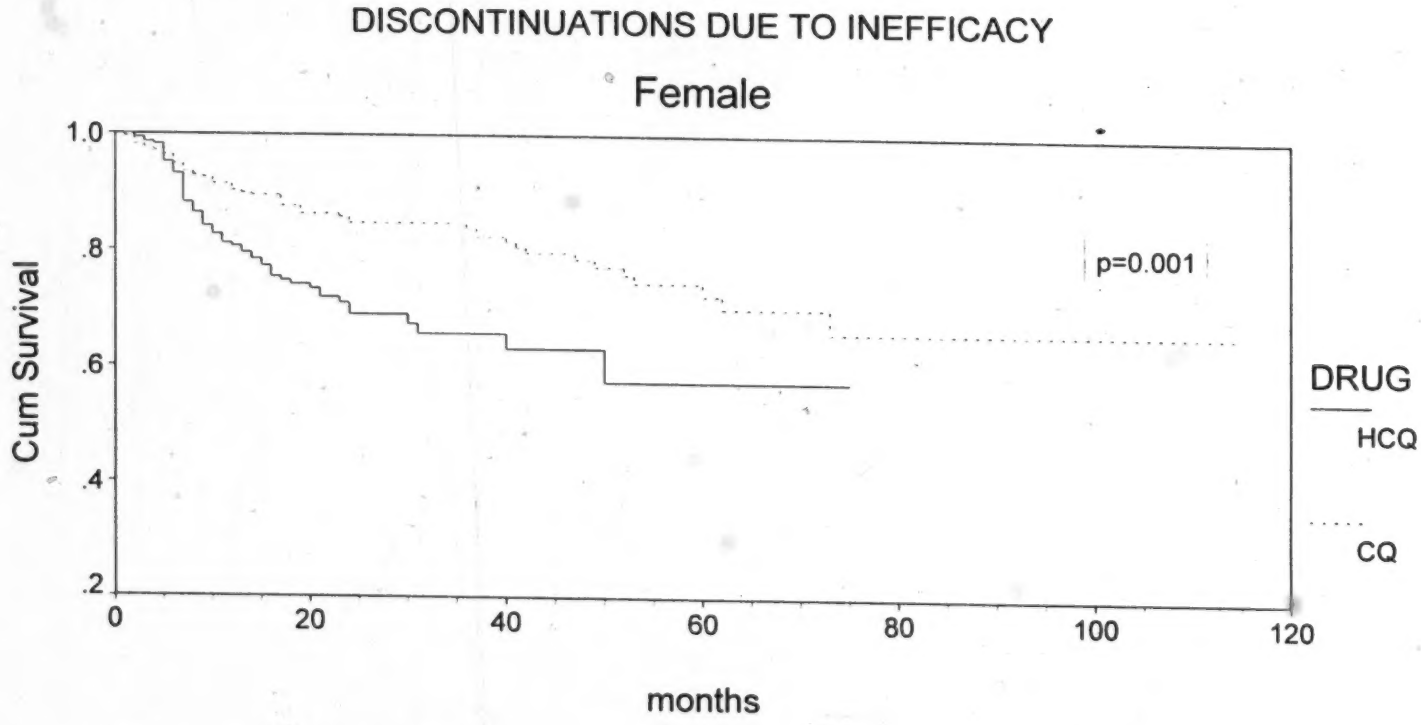

Figure 6.27 Kaplan-Meier curves for discontinuations due to inefficacy in females by drug.

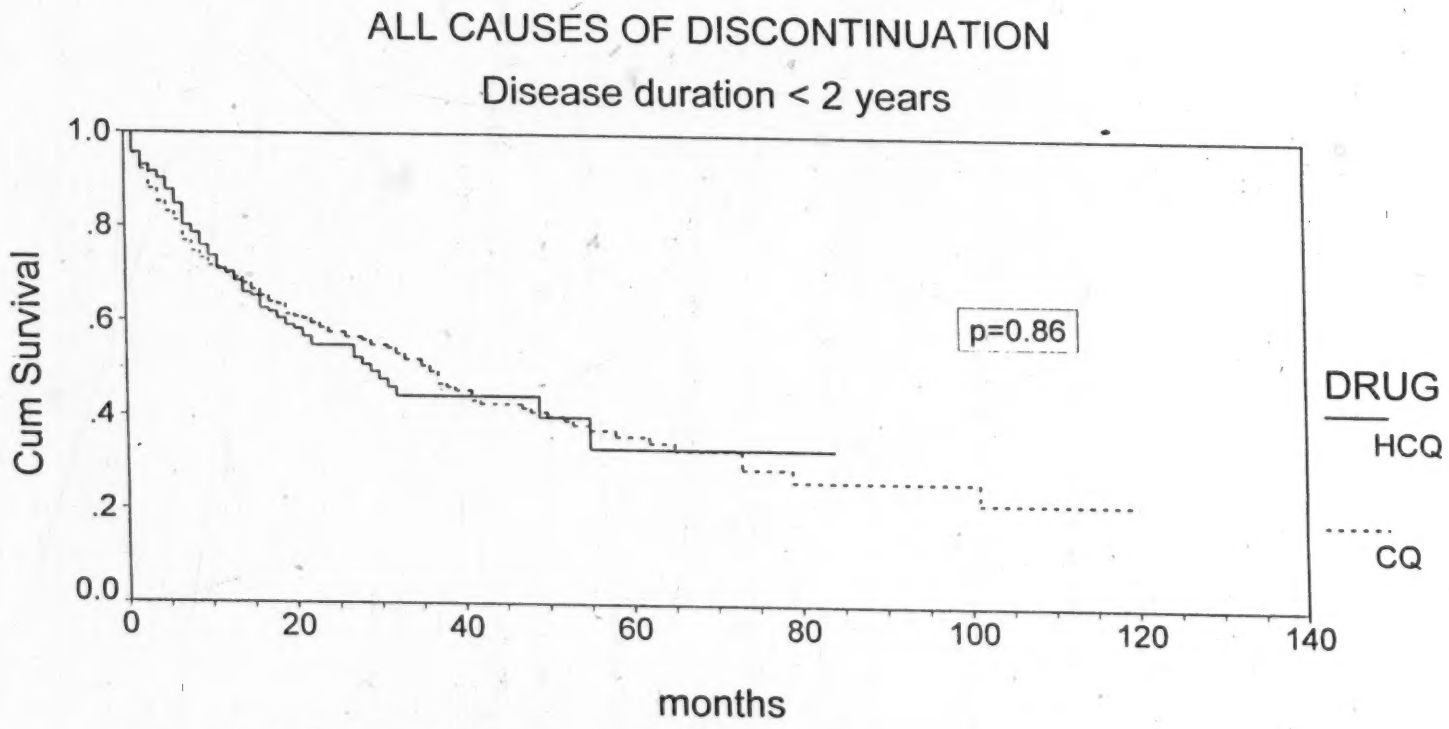

Figure 6.28 Kaplan-Meier curves for discontinuations due to inefficacy by drug and disease duration

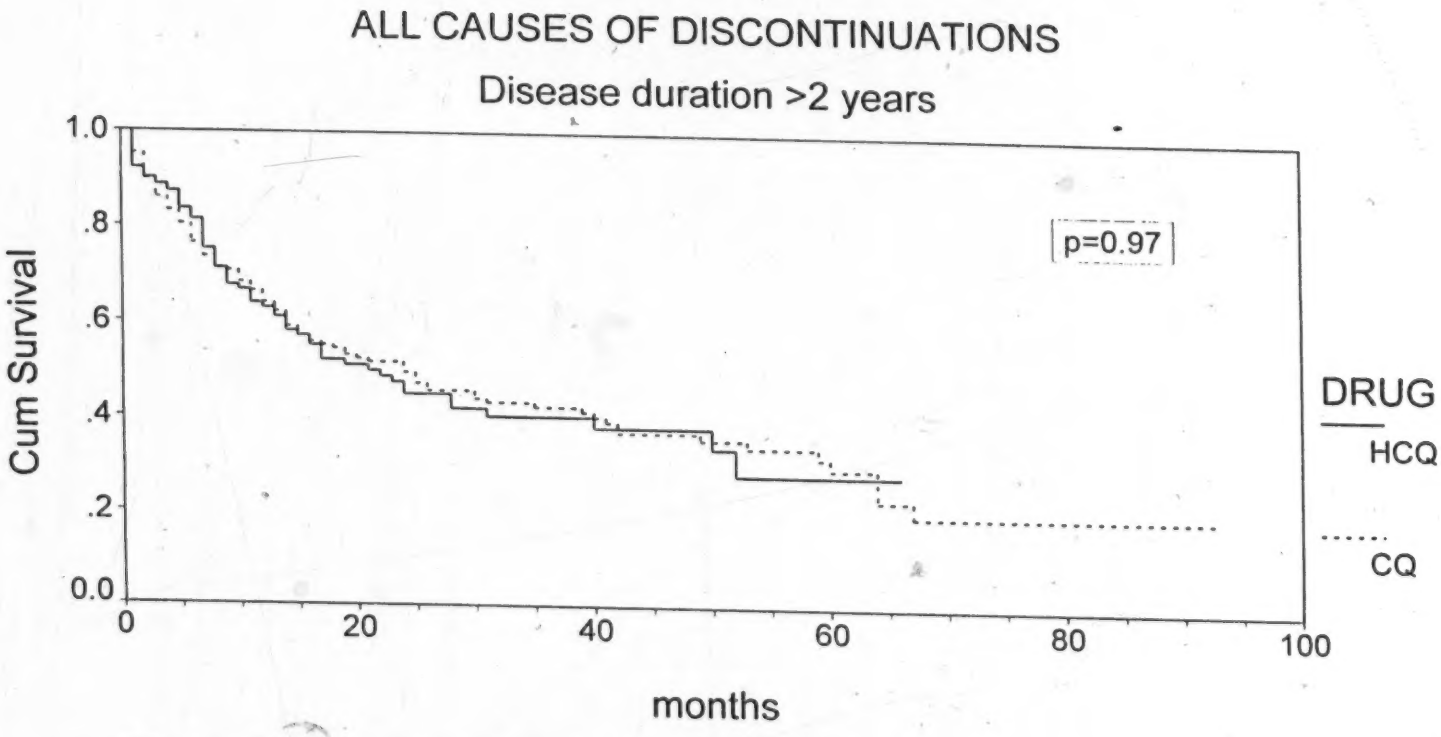

Figure 6.29 Kaplan-Meier curves for inefficacy discontinuations by type of antimalarial and disease duration.

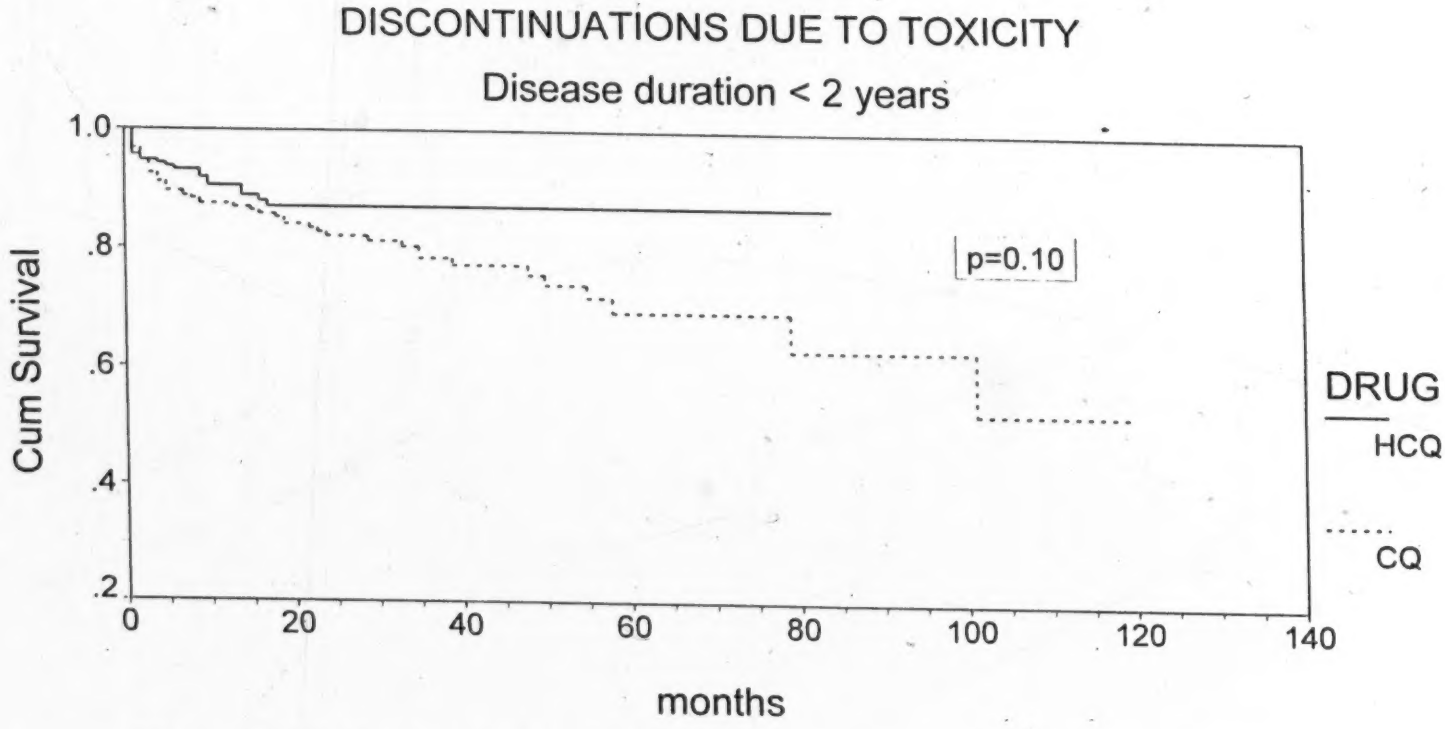

Figure 6.30 Kaplan-Meier curves for discontinuations due to toxicity by drug and disease duration

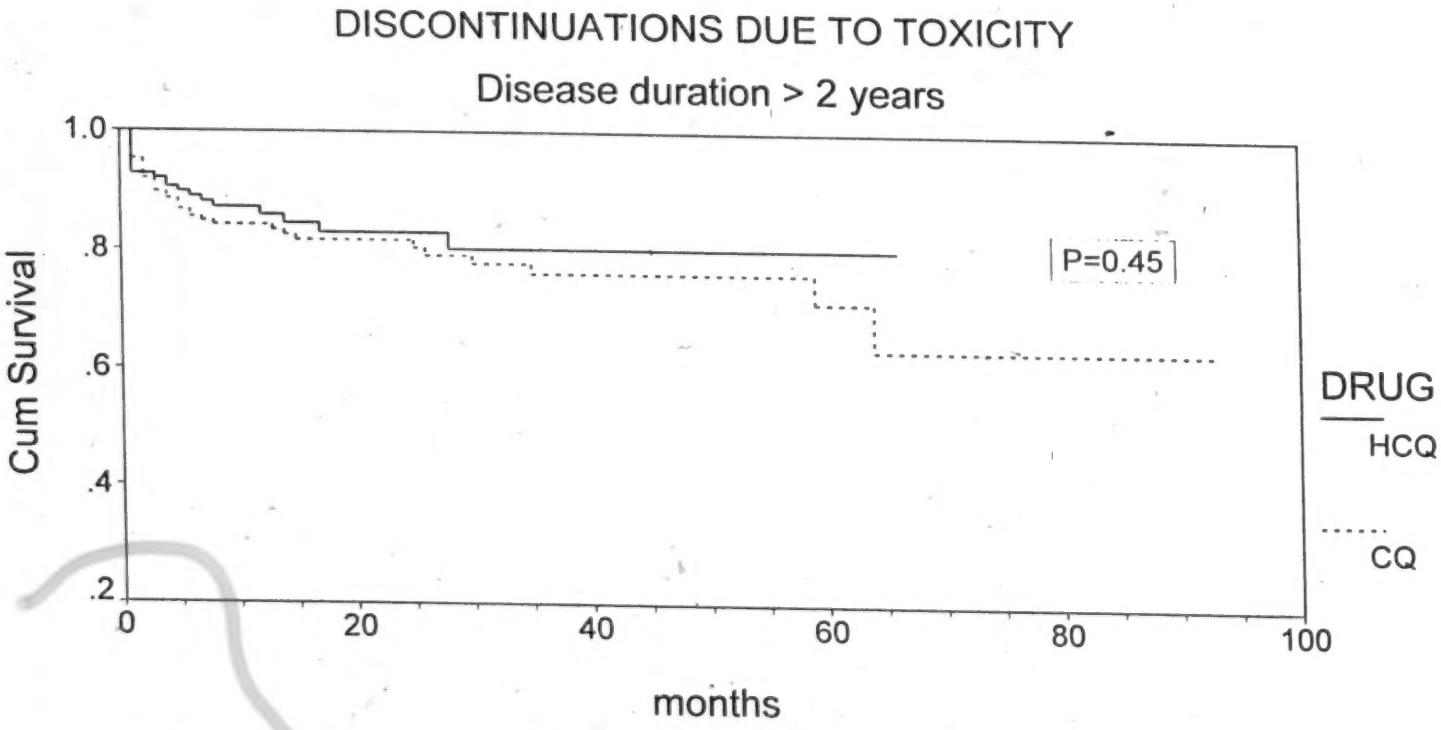

Figure 6.31 Kaplan-Meier curves for discontinuations due to toxicity by drug and disease duration

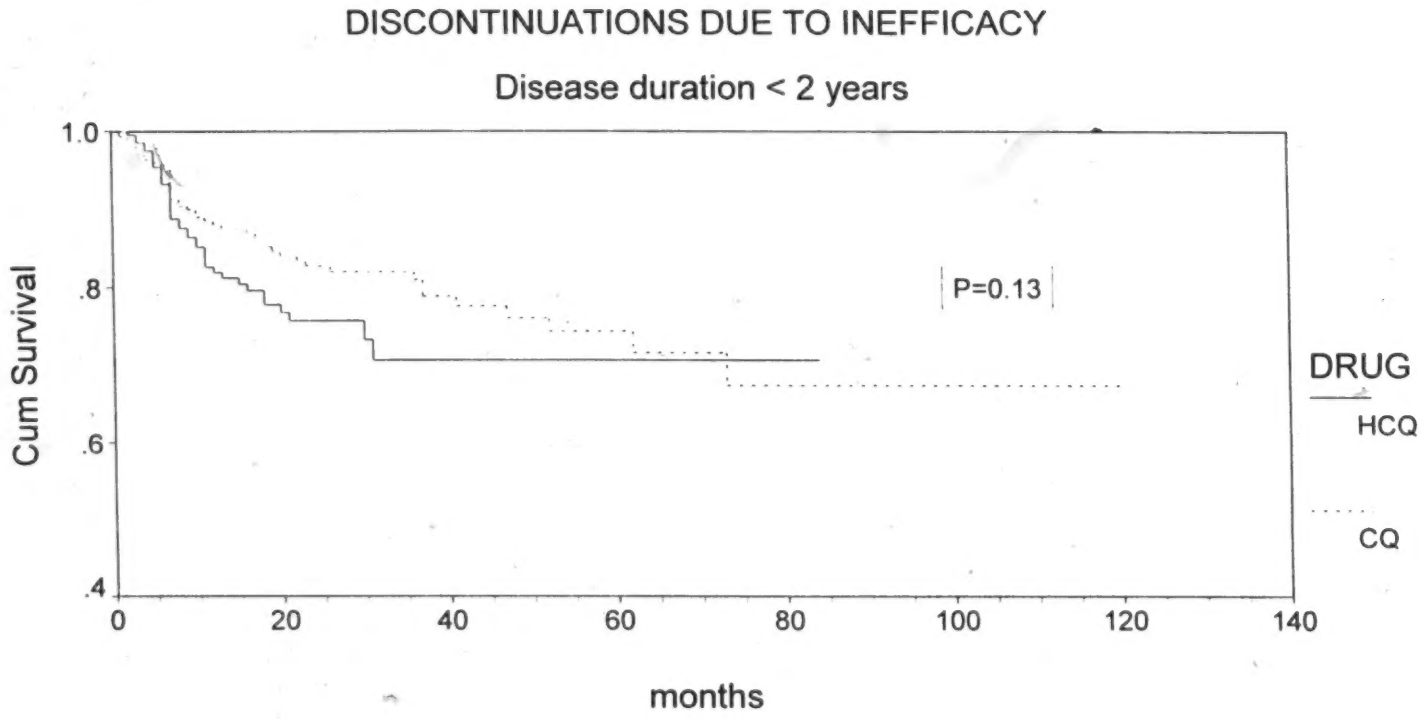

Figure 6.32 Kaplan-Meier curves for discontinuations due to inefficacy by drug and disease duration

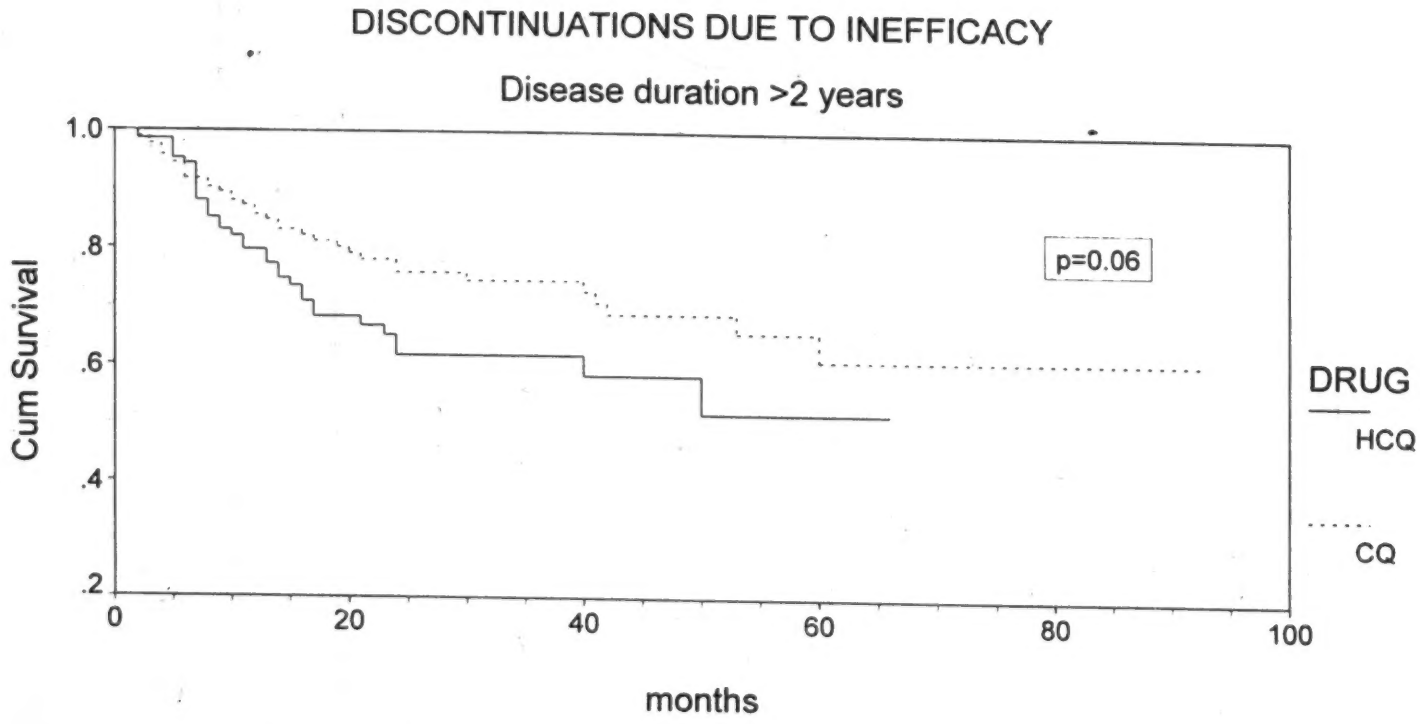

Figure 6.33 Kaplan-Meier curves for inefficacy discontinuations by type of antimalarial and disease duration of more than 2 years

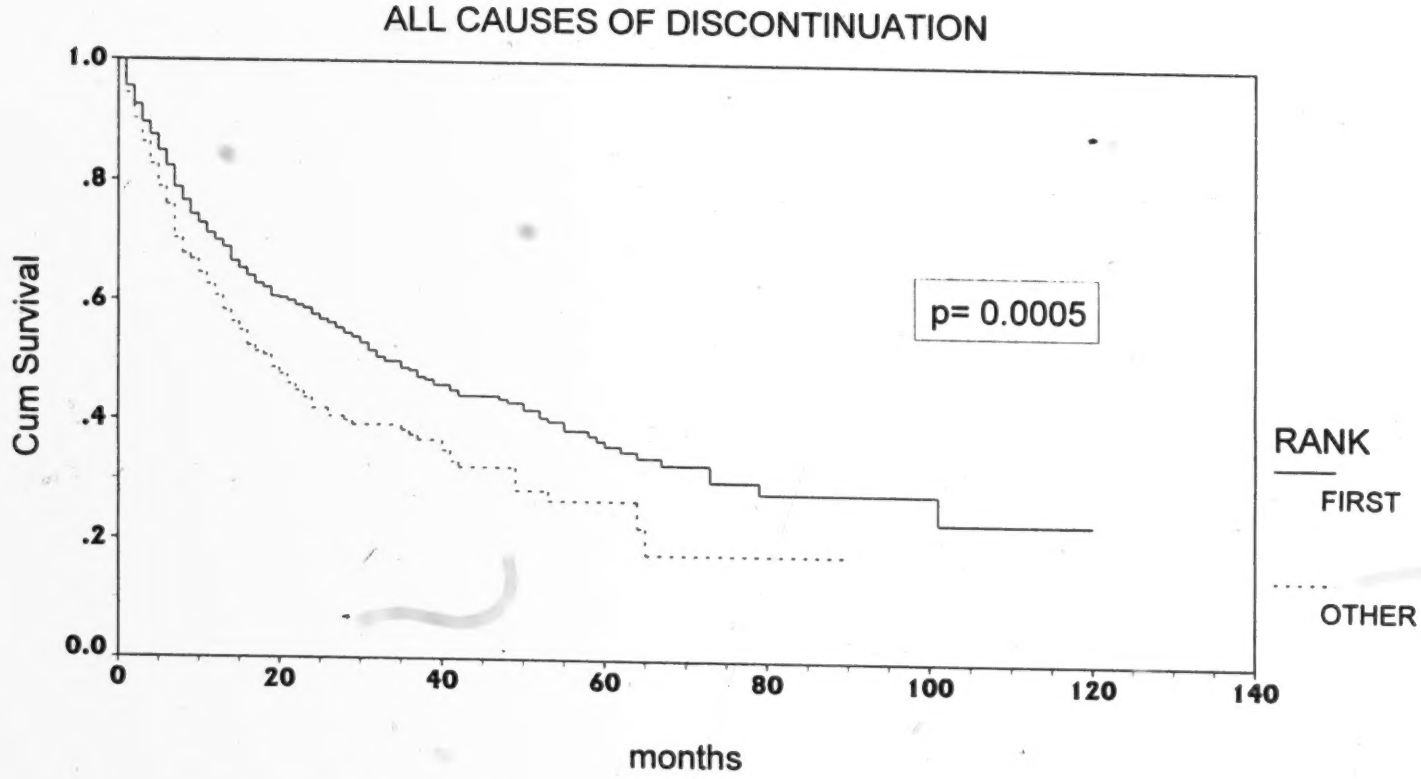

Figure 6.34 Kaplan-Meier for all causes of discontinuation by rank.

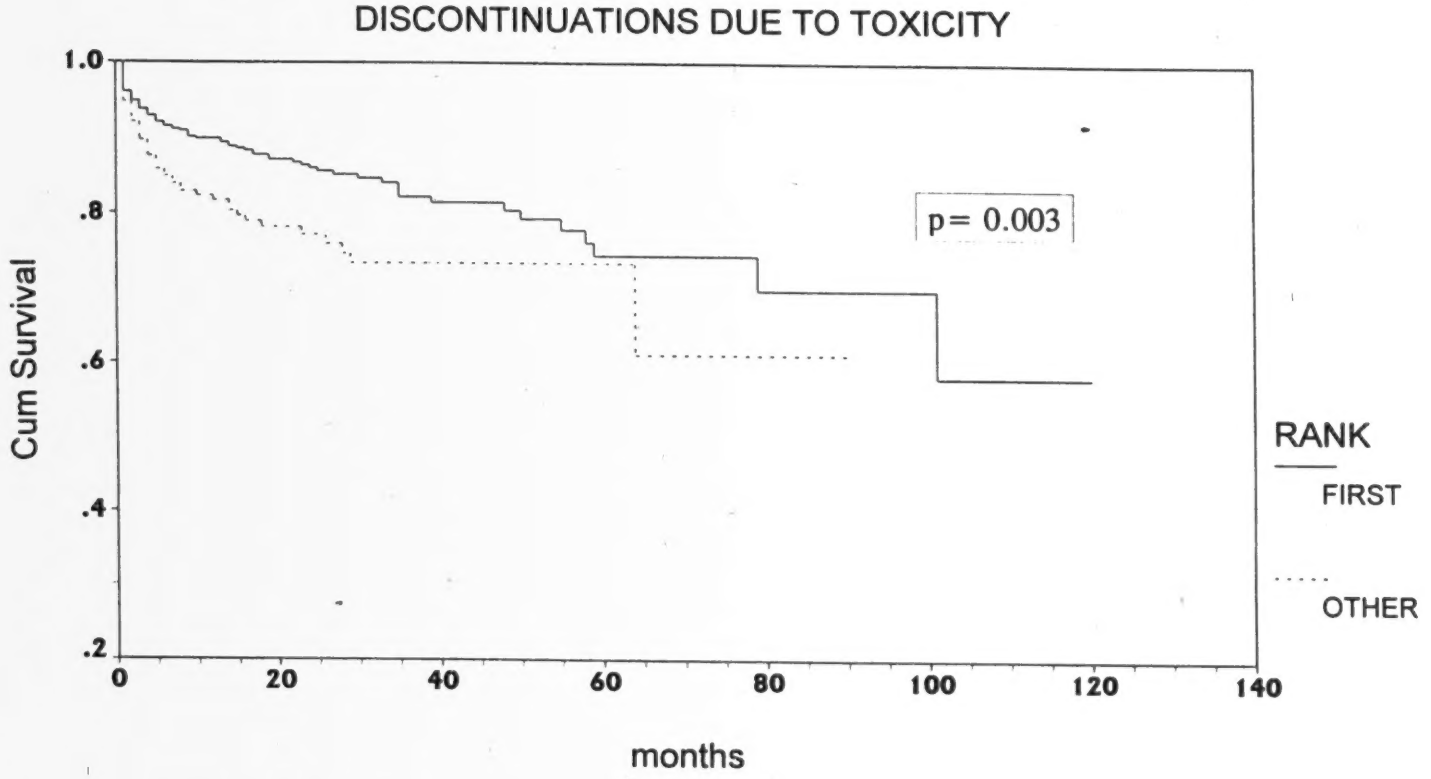

Figure 6.35 Kaplan-Meier for discontinuations due to toxicity by rank.

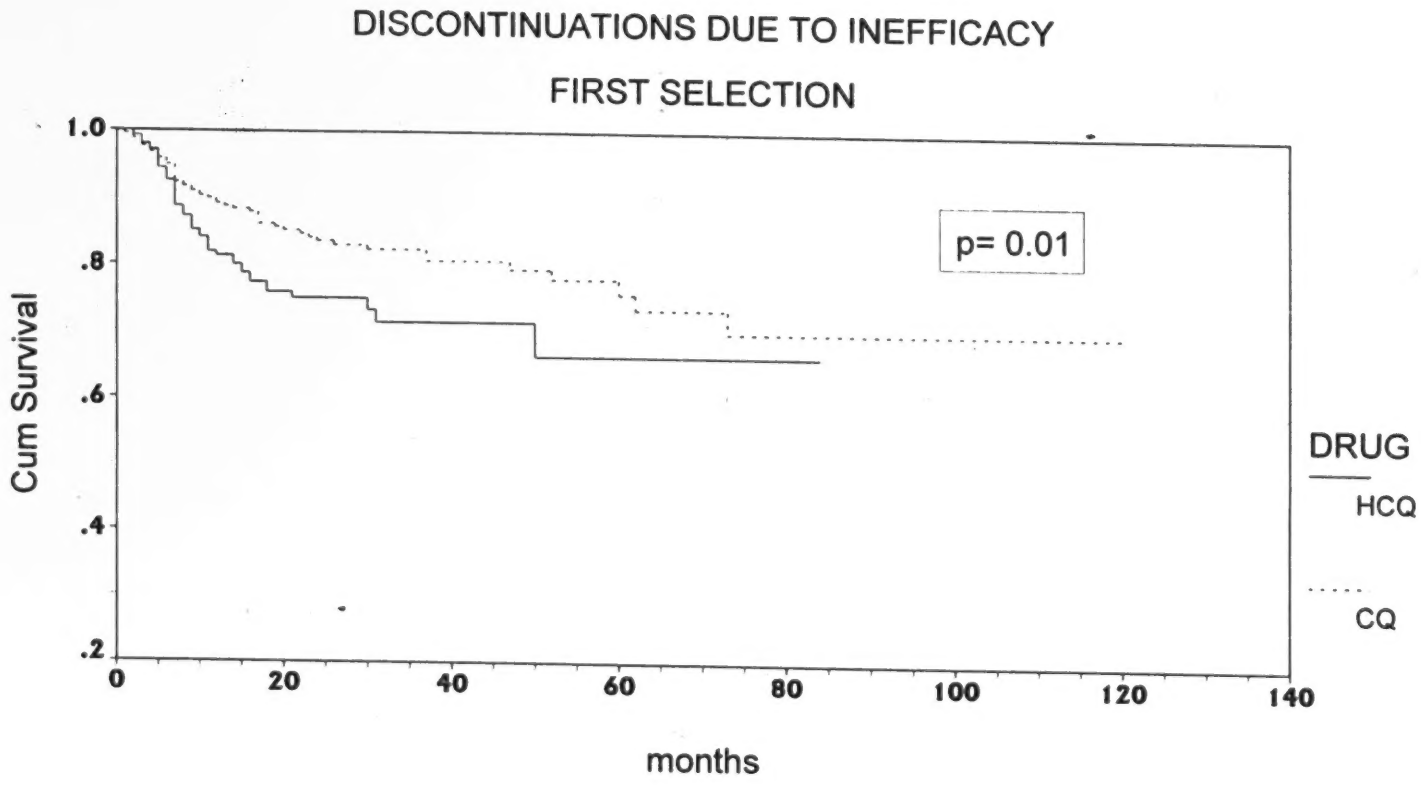

Figure 6.36 Kaplan-Meier for first rank selection by type of AM.

CHAPTER 7

RESULTS 3

MULTIVARIATE ANALYSIS

COX REGRESSION

The Cox regression model was used to examine the associations of different variables with the outcome of AM therapy (e.g.; overall, toxicity, and inefficacy discontinuations). Varables were all treated as categorical.

-Gender: gender was entered as dichotomous variable:

0= male

1= female

- Disease:

1= rheumatoid arthritis

2= systemic lupus erythematosus

3= palindromic arthritis

4= other

- Rheumatologist:

1= rheumatologist 1

2= rheumatologist 2

3= rheumatologist 3

4= rheumatologist 4

5= rheumatologist 5

6= rheumatologist 6

7= other rheumatologist

- Type of AM:

0= CQ

1= HCQ

- Rank:

0= selection other than first

1= first selection

- Age in years: age at the onset of antimalarial therapy was entered as a dichotomous variable (it has normal distribution) using the mean as the midpoint to create two categories.

0= less than 46 years

1= higher than 46 years

- Disease duration:

0= less than two years of disease duration

1= more than two years of disease duration

All models treated th "0" category as baseline. So far the HCQ-CQ comparison, a hazard ratio (HR) greater than 1.0 means a greater rate of discontinuation in the HCQ group.

The purpose of using the Cox's regression model was to adjust for potential confounders. Thus, in the Kaplan-Meier method, evaluation for a single variable is made, but it is likely that other variables may also explain the variation in the hazards for discontinuations. Therefore, a multivariate analysis which takes into account censored observations is mandatory. Predictors for three separate outcomes were evaluated: a) all causes of discontinuations, b) toxicity discontinuations, and c) inefficacy discontinuations.

The assumption of proportional hazards for the main outcome measure (all discontinuations, toxicity and inefficacy discontinuations) was tested by plotting the **log [-cumulative hazard]** (Figure 7.1 to 7.3). The survival curves are approximately equidistant, indicating that, for all causes of discontinuation

as endpoint, the proportional hazard assumption is satisfied (Figure 7.1). Similar results were found for toxicity and inefficacy (Figures 7.2 and 7.3).

1. ALL CAUSES OF DISCONTINUATION

Initially all the variables listed above were modeled individually (univariate) and results are shown in table 7.1. Type of AM was not a statistically significant predictor. This was in agreement with the results seen in the Kaplan-Meier analysis for this outcome variable. A second model was tested keeping all the variables mentioned above in the model as main effects regardless of their level of statistical significance in the univariate analysis (Table 7.2). Here, only disease type and rheumatologist were the statistically significant predictors. Again, type of AM was not a significant predictor for all causes of discontinuations. Those other variables which were initially significant in the univariate analysis may be considered as confounders since they were not significant in the second model. A third model was built, this was an investigator-driven model with the purpose of finding the variables which explained most of the variability of the dependent variable. This model was built using the -2 log likelihood ratio test as method for comparison and selection of the variables as well as the models (Table 7.3). Using this approach, disease type and physician were the only significant predictors. Results of this model are consistent with those seen in the second model and with the Kaplan -Meier. Therefore our variable of interest (type of AM) was not a statistically significant predictor. Thus, if all causes of discontinuations (including inefficacy and toxicity) are used to evaluate effectiveness, then there are no differences between CQ and HCQ in this respect. Finally a fourth model starting with model in Table 7.2 was built taken interactions in addition to the main effects. Here, disease type and physician remained as significant predictors, but there was a significant interaction between physician and type

of AM. However, the hazard ratios and coefficients did not show a dramatical change with respect to those seen in the model not taking interactions into account. Therefore, a preference for the model of Table 7.3 should be made.

2. DISCONTINUATIONS DUE TO TOXICITY

The same independent variables and the same approaches were used to built the models for AM discontinuations due to toxicity. Table 7.5 shows the results of all variables when they were tested as independent variables one at the time (univariate). Rank selection and age at the onset of AM therapy were the only significant predictors. However, other variables such as disease type, gender, and rheumatologist showed marginal statistical significance. Of interest, type of AM was not a significant predictor variable. However, when all variables were included as main effects, type of AM became a significant predictor (Table 7.6). Thus, HCQ had less chance of discontinuation due to toxicity than CQ (HR=0.57, 95%CI 0.37-0.90). In addition, older patients (more than 46 years of age) had higher hazard rates of discontinuation due to toxicity than younger patients (less than 46 years of age at the onset of AM therapy). However, physician had a marginal statistically significance (p= 0.06). When the investigator driven model was used to build the best model, type of AM ,rank selection, physician, age at the onset of AM therapy were the only statistically significant predictors (Table 7.7). Here, HCQ had again lower hazard rates of discontinuation due to toxicity (HR= 0.62, 95%CI 0.40-0.96). These results are in agreement with the curves seen in the Kaplan-Meier for these variables. Thus, the same variables were statistically significant in both analyses with the exception of type of AM which did not reach a statistical significance. Moreover, those variables that were not statistically significant in the Kaplan-Meier remained as such in the final model. Finally, a model including interactions were built. Here, only rank

and age persisted as a significant predictors in addition to interaction between physician and type of antimalarial. Of interest, type of AM was not longer significant. Again the coefficients and its corresponding hazard rates did not change dramatically in comparison to those seen in model 3 (best model with no interactions). This suggest than a model with no interactions should be preferred. Moreover, a high correlation between physician and type of AM is expected due to the AM preferences.

3. DISCONTINUATIONS DUE TO INEFFICACY

Finally, the same variables and methods were used for discontinuations due to inefficacy. Table 7.9 shows the results of the univariate analysis (each variable as a single predictor). Here, all variables but physician and age at the onset of AM therapy were statistically significant. HCQ had a higher rate of discontinuation than CQ (HR= 1.4; 95% CI 1.09-1.99). When all variables where entered into the model regardless of their level of significance in the univariate analysis, only disease type was statistically significant (Table 7.10). Again, HCQ had higher rates of discontinuation due to inefficacy in comparison to CQ, however, this did not reach a statistically significant difference (HR= 1.35; 95%CI 0.89-2.04). Nevertheless, type of AM was one of the variables which fitted the best model (Table 7.11). Thus, HCQ had a higher rate of discontinuation due to inefficacy (HR= 1.44; 95% CI 1.06-1.96). All the three variables selected in this model (type of AM, disease type, and gender) were the only ones which were significant in the Kaplan-Meier analysis (Figures 6.6, 6.21, and 6.27). Finally a fourth model buit from model which included interaction was tested (Table 7.12). Here main effects of type AM were not significant, but there was a significant interaction between type of AM and gender. Since there is no biological evidence to sustain this interaction, the model with nointeractions must be prefered.

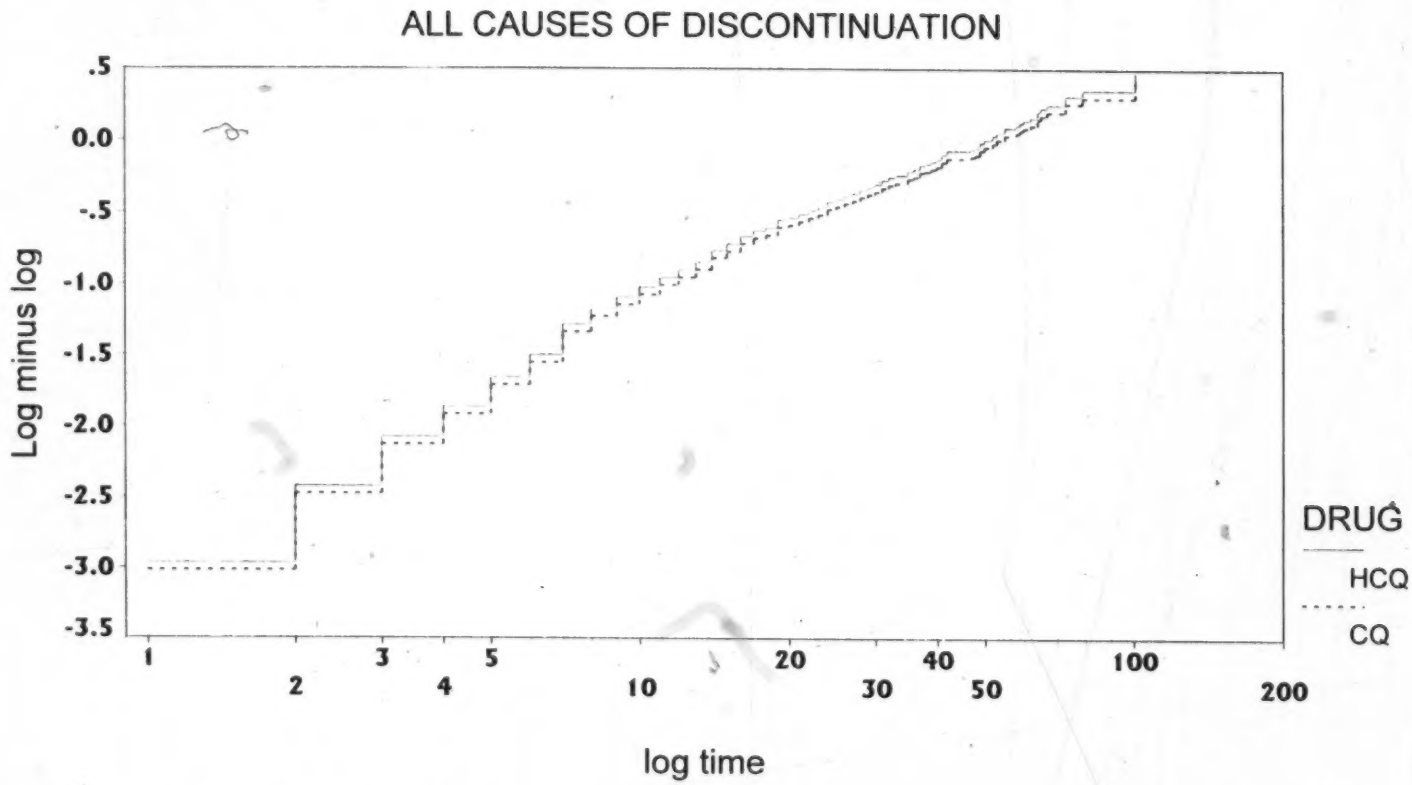

Figure 7.1 Graph of log {-log [S(t)] } against log time by type of AM.

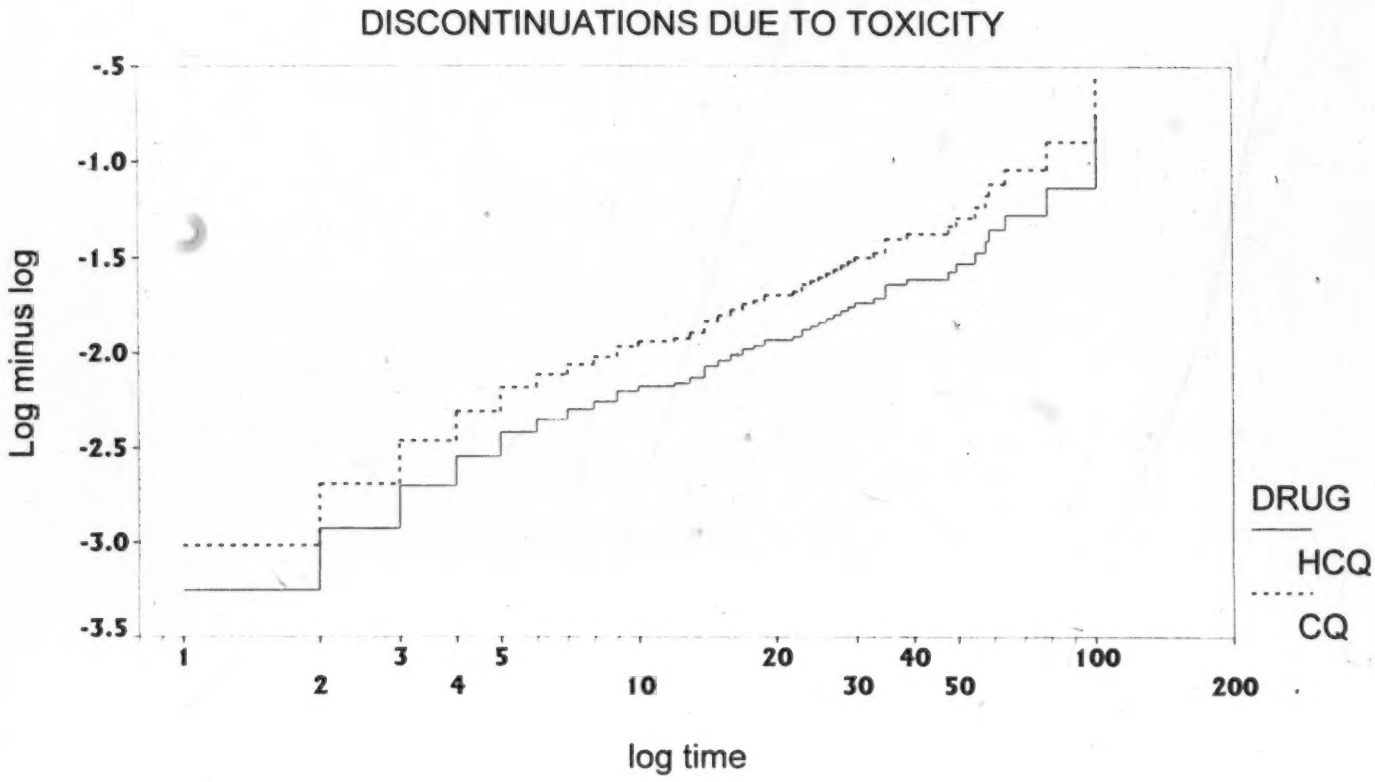

Figure 7.2 Graph of log{ -log [S(t)] } against log time by type of AM.

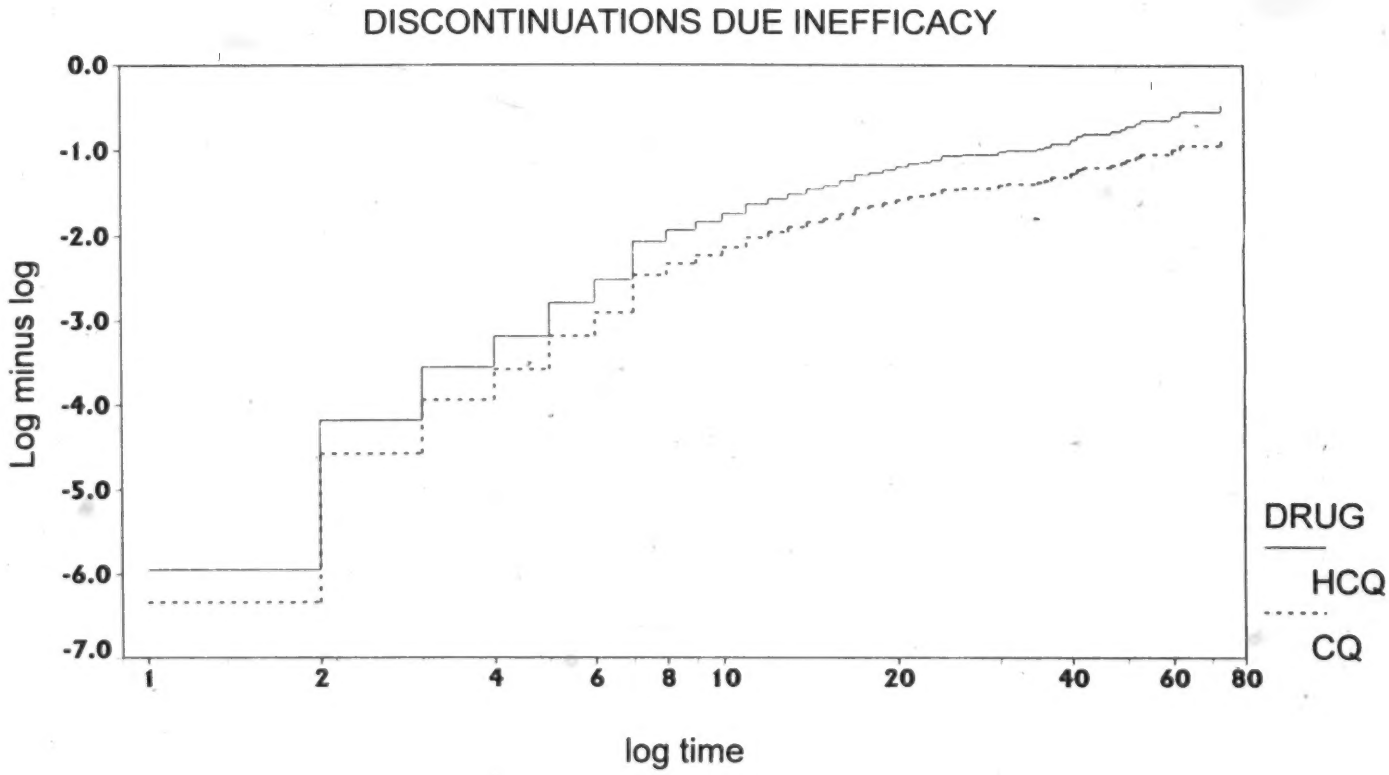

Figure 7.3 Graph of log{ -log [S(t)] } against log time by type of AM.

Table 7.1 Cox regression model (univariate) with all causes of discontinuation as dependent variable. Each one represents a separate model with a single main effect.

ALL CAUSES

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	-0.05	.09	1.05	0.87 -1.28	0.58
Rank (first)	0.34	.10	1.40	1.16 -1.71	0.0006 *
Disease (RA)					0.0006 *
Age (<46 yrs)	0.22	.09	1.25	1.03 -1.50	0.02 *
Sex (male)	-0.08	.11	0.91	0.74 -1.14	0.44
Disease duration (< 2 yrs)	0.20	.09	1.22	1.01-1.50	0.03 *
Physician (Rh1)					0.03 *

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.2 Cox regression model (all variables) with all causes of discontinuation as the dependent variable.

ALL CAUSES

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	-0.19	.13	0.83	0.65 - 1.06	0.14
Rank (first)	-0.11	.13	0.89	0.69 - 1.17	0.41
Disease (RA)	-----	---	----	----------	0.02 *
SLE	-0.49	.16	0.60	0.44 - 0.83	0.002 *
PA	-0.19	.16	0.82	0.59 - 1.14	0.24
Other	-0.17	.19	0.83	0.57 - 1.23	0.37
Age (< 46 yrs)	0.07	.10	1.08	0.87 - 1.32	0.48
Disease duration (2 yrs)	0.09	.11	1.09	0.87 - 1.37	0.41
Physician (Rh1)	---	---	----	----------	0.05 *

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: standard error

Table 7.3 Cox regression model (best model) with all causes of discontinuation as dependent variable.

ALL CAUSES

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Disease (RA)					0.02 *
SLE	-0.58	.13	0.56	0.43 - 0.77	0.001*
PA	-0.30	.15	0.73	0.55 - 0.99	0.04 *
Other	-0.25	.19	0.77	0.55 - 1.11	0.16
Physician (Rh1)					0.01 *

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: standard error

Table 7.4 Cox regression model (best model with interactions) with all causes of discontinuations as dependent variable.

ALL CAUSES

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Disease (RA)					0.0002 *
SLE	-0.57	.14	0.56	0.43 - 0.73	0.001*
PA	-0.29	.15	0.75	0.55 - 1.006	0.05 *
Other	-0.26	.19	0.77	0.54 - 1.11	0.17
Physician (Rh1)	----	---	----	----------	0.01 *
Physician X AM (°)	----	---	----	----------	0.0008 *

(°) Interaction between rheumatologist and antimalarial
* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: standard error

Table 7.5 Cox regression model (univariate) with discontinuations due to toxicity as the dependent variable.

	TOXICITY				
Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	-0.23	.17	0.78	0.55 -1.11	0.18
Rank (first)	-0.49	.17	0.60	0.43 - 0.85	0.004 *
Disease					0.11
Age (<46 yrs)	0.66	.17	1.95	1.38 - 2.74	0.0001 *
Sex (male)	0.36	.22	1.44	0.93 - 2.21	0.10
Disease duration (< 2 yrs)	0.21	.17	1.24	0.88 - 1.74	0.21
Physician (Rh1)					0.06

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.6 Cox regression model (all variables) with discontinuations due to toxicity as the dependent variable.

TOXICITY

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	-0.54	.22	0.57	0.37 - 0.90	0.01 *
Rank (first)	-0.29	.22	0.74	0.47 - 1.16	0.19
Disease					0.94
Age (<46 yrs)	0.63	.19	1.88	1.28 - 2.75	0.001 *
Sex (male)	0.36	.22	1.54	0.97 - 2.43	0.10
Disease duration (< 2 yrs)	0.007	.19	0.99	0.67 - 1.45	0.21
Physician (Rh1)					0.06

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.7 Cox regression model (best model) with discontinuations due to toxicity as the dependent variable.

	TOXICITY				
Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	-0.46	.21	0.62	0.40 - 0.96	0.03 *
Rank (first)	-0.34	.18	0.70	0.49 - 1.00	0.05 *
Age (<46 yrs)	0.60	.17	1.83	1.29 - 2.59	0.0006 *
Physician (Rh1)	----	---	----	----------	0.07

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.8 Cox regression model (best model with interactions) with discontinuations due to toxicity as the dependent variable.

TOXICITY

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Physician X type of AM	----	---	----	----------	0.0008 *
Rank (first)	-0.38	.18	0.70	0.47 - 0.98	0.04 *
Age (<46 yrs)	0.57	.18	1.77	1.25 - 2.52	0.001 *

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.9 Cox regression model (univariate) with discontinuations due to inefficacy as the dependent variable.

INEFFICACY

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	0.39	.15	1.4	1.09 - 1.99	0.01 *
Rank (first)	-0.59	.15	0.55	0.40 - 0.75	0.0001 *
Disease (RA)					0.0001 *
SLE	-1.4	.29	0.25	0.14 - 0.44	0.0001 *
PA	-0.47	.24	0.62	0.39 - 1.0007	0.05 *
Other	-0.43	.29	0.65	0.36 - 1.16	0.14
Age (<46 yrs)	0.15	.15	1.16	0.86 - 1.56	0.32
Sex (male)	-0.38	.16	0.68	0.49 - 0.94	0.02 *
Disease duration (< 2 yrs)	0.33	.15	1.3	1.02 - 1.89	0.03 *
Physician (Rh1)	----	---	---	----------	0.12

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.10 Cox regression model (all variables) with discontinuations due to inefficacy as the dependent variable.

INEFFICACY

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	0.29	.21	1.35	0.89 - 2.04	0.15
Rank (first)	-0.23	.20	0.79	0.53 - 1.18	0.24
Disease (RA)					0.0001 *
SLE					
PA					
Other					
Age (<46 yrs)	-0.21	.16	0.81	0.58 - 1.12	0.19
Sex (male)	-0.31	.18	0.73	0.52 - 1.04	0.08
Disease duration (< 2 yrs)	0.17	.18	1.19	0.83 - 1.71	0.33
Physician (Rh1)	----	---	----	----------	0.24

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.11 Cox regression model (best model) with discontinuations due to inefficacy as the dependent variable.

INEFFICACY

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM (CQ)	0.37	.15	1.44	1.06 - 1.96	0.01 *
Disease (RA)					0.0001 *
SLE	-1.36	.29	.25	0.14 - 0.45	0.0001 *
PA	-0.41	.24	0.66	0.41 - 1.07	0.09
Other	-0.42	.29	0.66	0.37 - 1.16	0.14
Sex (male)	-0.35	.16	0.70	0.51 - 0.97	0.03 *

* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

Table 7.12 Cox regression model (best model with interactions) discontinuations due to inefficacy as dependent variable.

INEFFICACY

Predictor (Reference category)	**B**	**SE**	**HR**	**95% CI**	**p value**
Type of AM					
Disease (RA)					0.0001 *
SLE	-1.36	.29	.25	0.14 - 0.45	0.0001 *
PA	-0.48	.25	0.62	0.38 - 0.99	0.05 *
Other	-0.45	.29	0.64	0.36 - 1.13	0.13
Sex & Type of AM (°)	-----	---	----	----------	0.009 *

(°) Interaction between gender and type of AM
* Statistically significant
B: regression coefficient
HR: hazard ratio
SE: Standard error

RESULTS 3

CHAPTER 8

CONCLUSIONS AND

DISCUSSIONS

The purpose of this study was to evaluate the long-term effectiveness of AM in general and specifically to compare the long-term effectiveness between CQ and HCQ in rheumatic diseases. We use the rates of discontinuations as a measure of effectiveness. The follow-up design was based on a retrospective cohort study.

It is accepted that clinical trials provide the best evidence with respect to efficacy and toxicity, however, almost exclusively they are of a short or medium term duration. Since most of the rheumatic diseases are progressive and long-standing diseases necessitating drug treatment for many years, long-term effects are difficult to assess with clinical trials.

Although some studies have evaluated long-term effectiveness of second line drugs (including AM) in RA, all of them have analyzed either AM as a single group or they have involved only a single AM (2-5, 51-53). Others have evaluated only short-term effects (<1 year) of a single drug (38-52).

The selection of patients was based on the use of antimalarials between January 1985 to July 1993 for a rheumatic disease which had to be diagnosed by a rheumatologist. The main outcome was the cause of discontinuation of the drug. In order to avoid selection bias we include only patients who started the drug for the first time during the period of study. Definitions and rules for data collection were set before the review of medical records to avoid bias. The cause of discontinuation was that stated by the treating physician in the medical record. In those cases where this was not stated the cause was registered as unknown and treated as a missing value in the analysis.

In general, the characteristics of the cohort are similar to those reported in descriptions of rheumatic diseases (2-5,31,34-52, 54-60). The female-male ratio was 3 to 1 and the mean ages for the several disease groups were: 52, 36, 42, and 41 for RA, SLE, PA, and other diseases respectively. In addition, the disease duration and rank order were also similar to those found in

previous studies, which confirms that when used AM are prescribed early, at least in RA. These figures are similar to those included in textbooks and reviews of rheumatic diseases, which suggest that no serious demographic biases occurred attributable to selection procedures.

1. OVERALL RATES OF DISCONTINUATION

Unfortunately, previous studies evaluating long-term effectiveness have been conducted only in patients with RA. Therefore comparisons with this study will be limited to RA. In this study we found that overall discontinuation at the time of data collection were 50% (54% for HCQ and 46% for CQ). Discontinuations due to toxicity were higher for CQ (18%) than HCQ (12%) and this was statistically significant. In addition, when RA was analyzed as single group, discontinuations due to toxicity were 22% and 13% for CQ and HCQ respectively. These results are similar to those reported by Wijnands (4), and higher than those reported by other authors (34,3). Finally, differences of discontinuations due to inefficacy were not statistically significant between CQ and HCQ. Although these differences might be important (clinically or statistically) they must be interpreted with caution, since no adjustment for time or other confounders is taken into account. Therefore, this bivariate analysis just suggested that there were differences between CQ and HCQ with respect to overall rates of continuation. Moreover this differences appear to be mainly to higher rates of discontinuation due to toxicity in the CQ group.

Ocular side effects and especially retinopathy had been the major concern in the use of AM therapy. Although, there is enough evidence to support that using proper dosage (CQ= 4 mg/kg/day and HCQ= 6.5 mg/kg/day) the risk is minimal (74-77). Overall we found 41 patients with corneal deposits. Thirty-eight (7%) of these received CQ and 3 (0.8%) HCQ. This prevalence is much lower than that reported by Esterbrook, who found

keratopathy in 95% and less than 10% of the patients receiving CQ and HCQ respectively (76). In contrast, Scherbel et al. evaluated 333 patients with RA who received AM therapy and reported a prevalence of 16% and 8% for CQ and HCQ respectively (77). In addition Rynes reported no corneal deposit in 99 patients receiving (75). Although corneal deposits are the main ocular side effect, it is well known that these are reversible after discontinuation of therapy and they are not associated with an increased risk to develop retinal toxicity (74-77).

2. DISCONTINUATIONS AND ADJUSTMENT FOR TIME

As mentioned above, adjustment for time must be taken into account . Therefore an analysis that take into account time will give better estimations of continuation rates. Using this approach (Kaplan-Meier) there were no differences in the rates of continuation between CQ and HCQ. When figures were analyzed by disease group no differences between CQ and HCQ were seen. RA had similar results than those reported in prospective studies (4,52). Unfortunately, there are no studies evaluating the long-term effectiveness of AM in SLE and PA. Therefore, it is difficult at this stage to make comparisons.

When causes of discontinuation were splited in two groups: 1) those due to toxicity and 2) those due to inefficacy, Kaplan-Meier curves for discontinuations due to toxicity were higher for CQ. In contrast HCQ had higher rates of discontinuation due to inefficacy. It is important to mention that in this analysis all causes of discontinuation but the one of interest were considered as censored. Moreover, all theses causes were independent of each other. It is possible that some patients discontinued for two reasons (e.g.; toxicity and inefficacy), however, from the medical notes this was not possible to obtain and only the reason of discontinuation stated by the treating physician was considered the main cause of discontinuation.

3. MULTIVARIATE ANALYSIS

Although Kaplan-Meier method adjust for time it does not adjust for other variables that may be of importance as predictors for continuation rates. Therefore, Cox's regression analysis was conducted for all causes of discontinuation, toxicity discontinuations, and inefficacy discontinuations to adjust for time and other confounders. Three models for each dependent variable were built. The first included all the potential confounders (either those suggested as important in the Kaplan-Meier analysis and those suggested as predictors in the literature) regardless of their statistical significance in the univariate Cox's analysis. Using this approach type of AM and gender were the only predictors which did not reach a statistical significant difference. In addition, in the second model (investigator-driven) where only the variables that best fit the data were selected; type of AM was still not significant. In fact, disease and physician were the only significant predictors. This was in agreement with the Kaplan-Meier results. Finally, when interactions were tested in the model type of AM remained as non predictor variable. However, a significant interaction between AM and physician was seen. Thus, AM are important depending on who prescribed it. However, a small variation in the hazard rates was seen between the model with no interactions and the one with interactions. In summary, type of AM is not important when all causes of discontinuation were evaluated.

Unlike to all causes of discontinuation, toxicity discontinuations were different for each antimalarial. Thus, when all variables were kept into the model HCQ had a lower hazard rates for discontinuations due to toxicity (HR= 0.57, 95% CI 0.37-0.90). Moreover, this differences persisted when only the variables which best fitted the data. However, when interactions were included in the model type of AM was significant depending on the physician who prescribed the AM. It is important to mention that values between the two

previous models showed small variation between them. Again small variation in the coefficients and hazard rates were seen with respect to the model without interactions. Finally, HCQ had higher rates of discontinuation due to inefficacy (HR= 1.4, 95%CI 1.06-1.96). When interactions were tested, AM had an interaction with gender. Again, these findings were consistent with the results obtained in the Kaplan-Meier analysis which may suggest that the models are robust.

Although this study was performed on a cohort assembled retrospectively and as a consequence missing information could be a major limiting factor, the number of missing values for the main outcome measure was low (2% in general for AM; 2% and 3% for CQ and HCQ respectively). Five percent of the patients had more than one cycle of AM therapy and we decided to analyzed only the first cycle to simplify the analyses. Thus, we were interested in the outcome of AM received for the first time. Moreover, including several outcomes in the same patient receiving the same drug at different times may produce bias, since patient could discontinue the drug early or later based on his/her previous experience with the drug. In addition, in those patients who received both AM only the first AM was included in the analysis. This was to avoid bias since the second AM would depend on which was the initial AM. In addition, toxicity would be the only reason to choose another AM since discontinuations due to inefficacy would hardly be associated with a second attempt with the other AM.

An important difference of this study with respect to those published previously was the disease duration (at least for RA). In this study mean disease duration at the onset of AM therapy in RA was 4 years. However, 60% had a disease duration of less than 2 years. When survival analyses were performed between disease duration of less than 2 years vs. more than 2 years a significant differences was seen. However, this variable was not a significant predictor in the multivariate analysis. In addition, in 72% of the

patients AM were the first drug of choice and this variable was a significant predictor in the multivariate analysis for all causes of discontinaution (Table 7.6). This is important since one of the major problems with the interpretation of observational studies is related to the fact that some of the drugs are given at different points in time with respect to disease course. Therefore, if given late the drug will have less chances of being efficacious since the disease may be less responsive to therapy. In fact various authors have reported that response to therapy is higher in patients with short disease duration (35, 42, 43). This might explain in part the higher survival in general seen in this study in comparison to those reported by other authors (3, 53, 54).

A limiting factor of this study was that we did not have baseline characteristics of disease to adjust for. However, there is no evidence to suggest that disease severity influenced the rheumatologists to prescribe one of the AM in preference to the other. This is more related to patterns of practice which we had previously documented in the rheumatologists who participated in the study as well as personal beliefs for AM prescription (78). Concomitant use of corticosteroids was not registered in the study and this could have contributed to the effectiveness. If this were the case then the effect of this probably would not be important since the use of corticosteroids by the specific rheumatologists participating in the study has been reported to be low (70). Another explanation for higher survival in this study could be that in Edmonton a previous study has shown that patients with RA are referred early for treatment. Moreover, family physicians refer most of their RA patients to the rheumatologist therefore the selection bias seen in most of the tertiary care centres are less evident in this study. Another factor may be the increased, universal, accessibility to medical services in Canada when compared to the USA, where most of the other studies evaluating long-term effectiveness are from.

In summary, in this study crude rates of discontinuations were different for each drug. The main cause of discontinuation for the AM in general and for HCQ was inefficacy 19% and 21% respectively. In contrast, the main cause of discontinuation for CQ was toxicity (18%). The multivariate analysis showed suggest that hazard rates for discontinuations due to toxicity are lower for HCQ (0.62, 95% CI 0.40-0.96) Hazard rates for discontinuations due to inefficacy were 1.4 times higher for HCQ. No significant differences exist between CQ and HCQ in terms of hazard rates for overall discontinuations. Therefore, long-term effectiveness between CQ and HCQ is similar. Nevertheless in the selection of AM a trade off by the clinician must be considered since hazard rates for toxicity and inefficacy are different between CQ and HCQ. Ocular and neuromuscular side effects occurred rarely and they were seen more often in patients who received CQ.

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APPENDIX 1
DATA COLLECTION FORM

ANTIMALARIAL STUDY

Name:_____**DOB(dd/mo/yr)**__/__/__**Sex:**____

Phone (H):_____**(B):**_____**Dr.**_____

Address:_____

RHEUMATOID ARTHRITIS CASE?: Yes___**No**___**Other:**_____

RA onset (mm/yr):___/___**RA diagnosis (mm/yr):**___/___**RF:**_____

Extraarticular features (describe):_____

Second line drugs previous to the onset of antilarials:

SLD	Onset (mm/yr)	Stop (mm/yr)	Reason
_____	____/_____	____/____	_____
_____	____/_____	____/____	_____
_____	____/_____	____/____	_____
_____	____/_____	____/____	_____
_____	____/_____	____/____	_____

SYSTEMIC LUPUS ERYTHEMATOSUS CASE? Yes___**No**____

SLE onset (mm/yr)___/___ **SLE diagnosis (mm/yr)** ___/___

Indication for antimalarials:(arthritis, rash, fatigue):_____

Second line drugs prior to antimalarials:_____

_____

Comments:_____

_____

Name_____ ID_____

PALINDROMIC ARTHRITIS: Yes___No___

Onset (mm/yr): ____/____ Diagnosis (mm/yr):____/____

Drugs prior to antimalarials_____

_____

Coments:_____

_____

TYPE OF ANTIMALARIAL: Chloroquine:___Hydroxychloroquine: ____

Both:____Continous___Discontinous____

Date of onset (mm/yr): ____/____ dose (mg/day): _____

Date of stoping (mm/yr) ____/____last dose (mg/day):_____

AM status at the last visit:_____ 1= still on

2= dc because of toxicity

3= dc because of inefficacy

4= dc for other reason_____

-1= unknown

MODIFICATIONS

1st (mm/yr): ____/____ from (dose)_____to _____reason_____

2nd(mm/yr): ____/____ from (dose)_____to _____reason_____

3rd (mm/yr): ____/____ from (dose)_____to _____reason_____

4th (mm/yr): ____/____ from (dose)_____to _____reason_____

Cumulative dose at the last visit (grams)_____

Did the patient had any side effect due to the AM used: Yes___No___

Name_____ **ID**_____

TYPE OF SIDE EFFECT?:	**OUTCOME?** dc perm, dc tempor, discon perman switched for another AM, decreas dose other.
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Has the patient ever seen by an ophthalmologist? Yes____ No____

If yes, Name of the ophthalmologist_____

Telephone:_____**Date last visit:**_____

Comments:_____

_____

_____